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THE

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OF THE MEDICAL SCIENCES

DECEMBER, 1929

ORIGINAL ARTICLES.

THE INFLUENCE OF RESEARCH IN BRINGING INTO CLOSER RELATIONSHIP THE PRACTICE OF MEDICINE AND PUBLIC HEALTH ACTIVITIES.*

By Theobald Smith, M.D.,

DIRECTOR OF THE DEPARTMENT OF ANIMAL PATHOLOGY OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, PRINCETON, NEW JERSEY.

The three concepts—research, medical practice and preventive medicine—contained in my theme represent three different states of mind. Constant application and time may have indelibly fixed and directed our mental outlook toward one of them. Or the mind in its growth may have risen above this one-phase state and combined in its mental outfit, two or even three of the phases typified by the three concepts. My task, however, is to keep them separate, for it is in the one-track mind that trouble arises from time to time as a result of conflict with the viewpoints external or alien to it. In taking this position I am compelled briefly to define what I understand by the terms public health, medical practice and research and their respective sphere of action. The concept of public health or preventive medicine is relatively new. If we go to the Century Dictionary of 1885 and its later supplements we will not find any definition of public health, although there are such expressions as public holidays, public indecencies, and others recorded. Nor do we find any mention of the expression preventive medicine although other medicines, such as cephalic medicine and logical medicine, are recognized. We do find the term sanitary science established: it is to show how the parasitic and other causes of disease may be avoided.

* Presented at a meeting of the Boards of Council of the Milbank Memorial Fund, held on March 13, 1929.

Even in the *Encyclopedia Britannica* of 1910 we find statements of public health laws, but nothing to indicate that the terms public health and preventive medicine had become crystallized out in definite form.

The present-day function of the medical practitioner is to relieve and palliate the pains of illness and to restore health. This is best understood if we take into account the evolution of medicine beginning with the dawn of human history. Two ideas seem to have dominated the physician—to ascribe disease to a cause and to search for a restorative remedy. The supernatural causes as interpreted by primitive society were gradually brought to earth and its enveloping atmosphere and last to factors internal and external to the patient himself. Today they are formulated as constitutional and environmental. Among the latter are microbic, dietetic, and other depressive factors. Public health and sanitation developed out of medical practice, its germ being the causal concept of disease, while medical practice became more directly concerned with the task of relieving distress in illness and applying empirically discovered means to restore normality to bodily functions.

Public health is thus the embodiment of the newer concepts of disease which assert that much of routine treatment has been ineffective, and sometimes injurious, and that the growing knowledge of causation forces preventive measures into the foreground. To determine causation and necessary conditions of disease a continuing analysis of disease phenomena is an essential requisite. Hence public health has its foundations in experimental, laboratory research and when it leaves the laboratory it takes its analytical methods into the field. Few epidemics can be traced to their source without the use of laboratory methods.

Research is fundamentally a state of mind involving continual reëxamination of the doctrines and axioms upon which current thought and action are based. It is, therefore, critical of existing practices. Research is not necessarily confined to the laboratory although it is usually associated with an elaborate technique and complex instruments and apparatus which require a laboratory housing. This is controlled research which endeavors to pick out of the web of Nature's activities some single strand and trace it towards its origin and its terminus and determine its relation to other strands. The older type of research involving observation and study of the entire fabric of disease largely with the help of the unaided senses, such as was the practice of doctors a century ago, has had its day, but backed by experience and a keen observant mind it even now occasionally triumphs over the narrow controlled research of the laboratory. It is the kind used by Darwin and other early biologists in establishing on a broad, comparative basis, the evolution of plant and animal life. Research is thus a vital part of

both medical practice and public health activities. It has become the fountain-head of the advances in both preventive and curative medicine. The bedside studies and the refined technique of the laboratory may still exist side by side when they do not clash. Many keen bedside observations are confirmed and reënforced by laboratory technique and many determinations in the laboratory are placed on a firm basis by the great experience of the physician. The technique of both preventive and curative medicine is thus created and remodeled from time to time by medical research. Both functions, though not its direct offspring, have been adopted and nurtured by it. Both are governed by its results in their operations.

When we come to the aims and objects of preventive medicine we find an entirely different motive power. It is the social consciousness and conscience which assumes control. Early public health activities emphasized the protection of the environment of the patient afflicted with a communicable disease rather than the patient himself. But both humanitarian and selfish considerations induced the community in the presence of certain diseases to take full charge of the patient. So we have as outgrowths of chiefly lay public health activities, the infectious-disease hospitals and the sanatoria for the tuberculous, to which both incipient and advanced patients are admitted. This incursion into the domain of the practising physician by bringing under one roof groups of patients affected with the same disease is met by a strong countercurrent from practice into preventive medicine. To appreciate this interchange, we must focus on the principle or doctrine which underlies both activities. This is briefly the projection of the results of civilized man's activities into the future. The idea of sowing and reaping, of planting and harvesting, with a period of patient waiting intervening, enters here. Futurity is an element of all medical practice today. Even in the actual presence of disease, the physician tries to interfere with the spread of the infectious agent in the body, its invasion of new tissues and organs. He tries to keep the virus localized, so as to reduce or prevent later injuries. He holds back secondary and superinfection. He studies the reactive capacities of the patient and tries to give them opportunity for maximum activity. He uses the vaccines and serums of laboratory origin, not necessarily to cure but to prevent further inroads and to mobilize latent capacities. All these procedures and measures have the element of the immediate or more distant future in them. They have almost entirely originated in laboratories devoted to public health, hygiene and sanitation. In brief, the treatment of disease has been gradually losing its character of emergency under the influence of research. The element of time and the natural recuperative capacity of the living tissues are more and more taken into consideration.

Medical practice has furthermore greatly gained in accuracy through the introduction of diagnostic methods of laboratory origin in the examination of blood and discharges. Individuals distributing disease promiscuously are readily detected. The causes of epidemics referable to the consumption of animal products, such as milk, have been brought to light to the benefit of medical practice.

Medical practice and preventive medicine apparently facing one another as competitors at the beginning of the bacteriologic era and getting their impetus from quite different medical theories and mental operations have been gradually drawn together willy-nilly by the force of truth developed by the underlying activities of research. This shows them to be after all of one substance, differentiated only by the points of attack. In the points of attack, however, minor differences become accentuated. Neither side able to see the whole may fall into error from time to time. The organizations devoted to problems of infectious diseases have seen only the microbe. The physician has seen the effects of heredity and special constitution in the variations between individual members of the same family in many reactions toward disease. He had been clinging to heredity in tuberculosis until dislodged by the bacillus, and now he is returning again to a modified view of heredity, with the bacillus in full view however. Preventive medicine looks with dismay on healthy carriers but the physician may regard them as normal. On the other hand, the physician realizes that there will always be disease, either of one kind or another, whereas the public health worker has dreams of completely suppressing infectious diseases.

Public health operations deal with mass phenomena and consequently must use statistics. The physician deals with the individual. Statistics are of little use to him, for his prognosis will probably depend on his own background of experiences. Even when he knows that 95 per cent undergoing a certain operation survive, this does not tell him whether his patient may not be one of the unfortunate 5 per cent. Public health doctrines are simple, but actual disease is very complex. Science seeks the simplest experimental conditions to determine truth, whereas practice inherits all the complications of Nature. The experiment assumes uniformity, the physician accepts diversity in his material. Both views are true in part only and each needs the other as a corrective. Thus diverging views conditioned by the field of work, the method of approaching it and the direction taken in it, lead naturally to a certain lack of appreciation of the respective functions of the other group. We might almost say they are tunnelling from two extremes into the mass of disease. Moreover the appreciation of the great mass of the lay public is often governed by superficial considerations. It has always been difficult to appraise properly the value of preventive

work. The surgeon who successfully deprives a patient of some recalcitrant organ receives more attention than one who should discover infection of drinking water in time to avert an epidemic. The countless casualties and catastrophies that do not happen as the result of anticipatory activities of preventive medicine would make fairy stories ordinary reading. They, however, have only a negative value in stimulating the appreciation of the public. To value prevention demands a sixth sense acquired only by a few. The highest achievement of civilized society is to be able to predict and prophesy and thereby control the immediate future.

That there should be some mutual lack of appreciation, some conflict of opinions between the two wings of the medical army may thus be taken for granted. Mutual criticism is uncomfortable but it is not an unmixed evil. It invites self-examination and correction of defects on the part of the more intelligent and makes for advance. Mere adulation does not involve any severe mental effort, but the discovery of defects implies observation and reflection on the part of the critic. The one who lauds does not need to prove his assertion, whereas the critic may be called upon to demonstrate the precise location of the weak spot he claims to have found. Concerning the relative merits of the two wings of medicine there need be no discussion for, like wings, they need one another to function and the community needs both. One function takes care of the accidents and casualties of life, the other peers just ahead to avoid those approaching. As long as disease prevails, the physician cannot be spared and disease will continue to exist for in the civilized world it, in its gravest forms, simply replaces the violence of Nature in removing the senile and the unfit. The physician is the outpost of the public health army. He is often the first to scent new diseases and to give warning of impending danger when he correctly diagnoses a case unexpected and out of the ordinary. He is the one to discover the spark, but it often requires unusual intelligence to do this sufficiently early. Public health cannot dispense with the supporting aid of practical medicine until the last case of some disease has been detected and restrained. It is the so-called last cases which will give most trouble to all agencies involved. They will be the most difficult to apprehend and the easiest to get out of hand and start new foci of disease unobserved.

It is not infrequently taken for granted that the results of laboratory research are final and its operations infallible. This, however, is far from true. The laws, theories, and inferences of experimental research are as subject to rectification as are inferences based on other human activities. They are approximations getting nearer and nearer the actuality with time. The methods of research may not be in error but the foundations of the experimental enquiries may have been inadequate. All research is based on so-called axioms

and postulates, the ultimate accuracy of which may be called in question and sooner or later subjected to investigation itself. In this way each generation provides more accurate supports. The change which our conceptions of such well-known diseases as diphtheria and tuberculosis have undergone in the past forty years is not easy to grasp because of its gradualness. Yet it is formidable. As long as disease exists, the operations of preventive medicine must be founded on our knowledge of disease. Health means no disease. Disease is the positive pole from which the current of research flows. It is not improbable that we shall be treated to some surprises in concepts of disease in due time which may make it desirable to reverse completely some of our present theories. We are thus forced to admit the fact that all human enquiries are narrow and partial. To include all conditions would require more than the Einstein type of mind to formulate the experimental attack. We must be satisfied with piecemeal work in the hope that occasionally some synthesizing genius will appear who can put the collected fragments together in some form acceptable to us and which will serve as a fresh pattern for further endeavors.

There is still another reason why humility of spirit should hover over our undertakings. In Nature everything is in a flux. Living things are changing. Nature is everywhere trying hundreds of experiments with the opportunities the human race is putting before her through the increasing flux and mobility of man and the things he controls. Out of this trial and error method come new diseases or new adaptations of existing ones. Epidemic flare-ups of well-known diseases come together with such apparently new developments as poliomyelitis, encephalitis and undulant fever. Just how these changes come about rests with future microbiologists coöperating with many other biologic and medical investigators. At present, we can only guess what the ultimate processes are, but it can scarcely be doubted that the ceaseless movement of the race is furnishing the occasions and trial combinations.

It was a happy conception to bring the resources of medical science and practice to play upon certain preventable diseases in a geographically defined community. The demonstration is a great experiment in the natural history of disease and a test of what modern medicine can do. The success of any large scale demonstration depends both upon the relative truth or accuracy of the fundamentals and the thoroughness with which they are applied in practice. If, for instance, the thorough application of what we are supposed to know of such a disease as tuberculosis fails to reduce its incidence in a population there is some unrecognized factor in the etiology. Our fundamentals, in other words, are not sufficiently close approximations to the reality. To demonstrate this would amply compensate for the extra expenditure of energy even if the demonstration was regarded as a failure.

The second requisite for securing the full benefits of a demonstration is the comprehensive and thorough application of the fundamental data in practice. To do this the demonstration must become a connecting link between the two kinds of activities, the preventive and the curative, for it must apply both the results of scientific research and the experience of the individual physician practising in a given territory and supposedly acquainted in general with the natural history of the population and the environmental conditions. It should bring together the student of public health and the local doctor.

The predominant hope involved in demonstrations, as well as the usual measure of success to be attained, is the numerical reduction in morbidity and mortality. We should, however, look somewhat beyond these goals and consider the demonstrations successful only if they teach us something we had not known before, something that can be applied to future experiments of which these are only the pioneers. How not to do a given task often ranks with or above positive instructions. In fact it is on a par with all health practice, the concealed motto of which is, how not to be sick. To insist on a general cleaning up of infectious disease as a result of the demonstration is to anticipate and discount in advance the experiment, for the demonstration is after all a great time experiment with modern concepts of prevention as the real issue. As I stated before, they must come in for test and rejuvenation from time to time in view of the changing condition of the entire world life, human, animal and plant.

Demonstrations are helpful in that they, in addition to their primary tasks, permit some light to play on the economic problems of disease. Though the physician sees them in the intimacy of the household, he has neither the time nor the means to bring his observations as a whole into the open and invite inferences and conclusions useful to the community. This the demonstrations may do if the accumulating material warrants it. It is the demonstration that is most prepared to tell from its special researches in what directions surplus means and energy may be spent with maximum returns in the form of health to the community. Finally, without the voluntary activities of lay groups entering the field of public health and these demonstrations which bring an entire population under the influence, spiritual and physical, of health principles, it would be well-nigh impossible to stimulate the interest of the public and create a so-called public opinion, which in the last resort is our dependence in assisting the inert mass of tradition, medical, legal and lay, to move a step forward.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA*

I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered after the Ingestion of Beef Muscle.†

By William B. Castle, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL, AND ASSOCIATE PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.)‡

It is the opinion of most physiologists and clinicians today that the secretory activity of the stomach is not indispensable to the continued well being and life of the individual.[1,2] This belief is the result of the practical observation that frequently large portions of the stomach, rarely even the entire organ, have been removed in animals and in man without apparent significant disturbance of the processes of digestion or assimilation;[3] and the idea possesses the theoretical basis that the enzymes of the intestine are apparently capable of carrying out for most proteins the digestion necessary to produce amino-acids.[4,5] It is, however, a fact known to clinicians that there are certain abnormal bodily states in which pathologic alterations of the secretions of the stomach may be encountered; and it has been suggested that a deficiency of the secretory function of the stomach might bear a relationship to the associated manifestations of disease.[6,6a] By far the most discrete of the conditions in which the question of the etiologic significance of a defect of the chemical function of the stomach has been raised, is Addisonian pernicious anemia. Since Grawitz[7] and others pointed out just before the beginning of this century the alteration of the gastric secretion, it has become recognized that a practically complete and constant absence of hydrochloric acid and of pepsin is found in nearly all cases of this disease.[8] For this and for other reasons to be given later, experiments on the gastric digestion of patients suffering from

* A preliminary report of this paper was read at the meeting of the American Society for Clinical Investigation at Washington on April 30, 1928.

† The expenses of this investigation have been met in part by grants from the Proctor Fund of the Medical School of Harvard University, for the study of chronic diseases, and by the gift of Mrs. Walter Fisher.

‡ This investigation has been made possible only by the coöperative work of many. It is a pleasure to acknowledge in particular my indebtedness to Dr. Herman A. Lawson of the Rhode Island Hospital, Providence, and to Dr. Angelo Scorpio for his assistance in the beginning of these experiments. The kind coöperation of Dr. Ralph C. Larrabee and Dr. William H. Robey of the Boston City Hospital, and the invaluable assistance of Miss Sylvia Warren, Mrs. Henry B. Cabot, Jr. and Miss Emilie Goode in making the blood studies, are gratefully acknowledged.

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pernicious anemia were undertaken in February, 1927, and are now described in this paper. The inherent difficulties of exact and prolonged clinical observation have been found great, but have not seemed to render unwise efforts possibly capable not only of shedding light on the cause of pernicious anemia, but also of yielding new information concerning the functions of the human stomach in respect to remote organs; particularly since the observations were of a chronic disorder not so far known to exist comparably in animals.

Consideration of the Possible Significance of the Achylia Gastrica. The almost universal incidence of an extreme reduction or absence of hydrochloric acid in the stomach contents of patients suffering from pernicious anemia has been established by the work of many observers.[8] Recently, by the use of new methods, it has become possible to demonstrate that this disturbance in these patients is remarkably great. The stomach of these individuals can be shown to be incapable of secreting acid even under the powerful stimulus of histamin subcutaneously injected;[9] and in contrast to the ability of the normal stomach to secrete various dyes after introduction into the blood stream is the total incapacity in this respect of the organ in pernicious anemia.[10] In a recent review of the literature bearing on the subject of the etiology of pernicious anemia, Cornell[11] concludes as follows: "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this, *the stomach contents do not contain free hydrochloric acid.*"

That this strikingly abnormal condition of the stomach may play an important rôle in the production of the disease has seemed probable to others.[6] In fact, the question of the relationship of the achylia to the disease has already received much attention in the literature, and accordingly only the most important bits of the accumulated evidence bearing on this matter will be considered.

In the distribution of the disease, there has been noticed in certain instances a notable tendency for it to occur in several individuals of the same family, and to reappear among their descendants.[12] Weinberg[13] has shown that a disproportionately large number of the unaffected members of such families show a reduction of the hydrochloric acid of the gastric contents. Furthermore, it is known on good authority that achlorhydria precedes all other symptoms of the disease, in a few instances by over ten years.[14] In certain individuals, the prolonged use of alcohol has been known to produce in some a temporary, in others a permanent achlorhydria.[6] The occasional appearance of pernicious anemia in association with an achlorhydria in chronic alcoholics is interesting from this point of view. Various clinicians here recognized that pernicious anemia may appear in association with cancer of the stomach in the presence of an achylia,[15] and since it has been possible in our experience to demonstrate the specific reaction of the disease under these circumstances to the liver extract of Cohn, Minot and their

collaborators,[16] it is possible to state with even more assurance that the anemia is of the Addisonian variety, and not therefore due to bleeding or metastases in the bone marrow. Strauss, Meyer and Bloom[17] have recently reported a case of gastric polyposis with achlorhydria which showed a blood picture consistent with pernicious anemia.

The case in Du Bois'[18] Clinic of a girl, aged thirteen years, who developed a typical pernicious anemia blood picture with achylia gastrica, is of unusual significance because the "spontaneous" appearance of the disease at this age is exceedingly rare. This little patient showed a typical remission following the administration of the liver extract just referred to; but since vomiting persisted in spite of the improvement of the blood, and since Roentgen rays showed pyloric obstruction, an exploratory laparotomy was performed. The operation revealed a constricting mass of tuberculous glands matted about the pylorus, an obstacle to gastric function that may well have produced the achylia, as in an adult a cicatrizing ulcer or scirrhous cancer in a similar site may do.

A test of the effect of complete lack of gastric juice could obviously be most certainly carried out if the entire stomach were removed. This remarkable operation had been performed in man and reported in the literature up to 1927 only ninety times, according to Miyagi.[19] Only 34 of these 90 patients were the subjects of total removal of the stomach in the anatomic sense, and recovered at least from the immediate effects of the operation. This author points out that strictly defining the performance of total gastrectomy as the ablation of the entire functional secretory portion of the stomach would probably greatly reduce the number of recorded successful attempts, since the technique by which that result could in reality be accomplished, would involve a division of the esophagus above the cardia. The physiologic significance of this requirement for a complete functional extirpation is obvious, since the cardiac end of the human stomach is richly supplied with glandular tissue. Recently Finney and Rienhoff[20] have reviewed the cases of gastrectomy in the literature. It is interesting that of the nine "total gastrectomies," which from the data given may fairly be assumed to have had a complete surgical removal of the stomach and subsequently survived over a year, 2 cases, those of Hartman and Moynihan, apparently developed pernicious anemia.

Hartman,[21] writing in 1921, states that until that date there was only one case of complete gastrectomy reported in the literature in which the subsequent history had been carefully followed for any length of time. That case was reported by Moynihan[22] as having enjoyed a good recovery for three years following the operation, but as then developing a "severe anemia" with which he died within a year. During the year he had one remission under treatment. An autopsy showed the features of severe anemia with the complete

absence of any recurrence of the primary malignant process of the stomach, or other cause for the lack of blood. The case which Hartman reports undoubtedly had a complete gastrectomy for "carcinoma of the cardiac end of the stomach with no glandular involvement," as was reported by the pathologist. He made a good operative recovery, but returned in about a year with gastric symptoms. Two years after operation the patient presented himself with the typical blood picture of pernicious anemia and some evidence of glossitis. A year later, while on a general diet containing, as it happened, some liver, the blood picture was still suggestive of pernicious anemia and the blood count lower. Dennig[23] has recently reported a case in which pernicious anemia with cord symptoms developed ten years after the complete removal of the stomach for a large ulcer. In this case a response to liver feeding was observed. Hurst[6] mentions three other cases of pernicious anemia as developing after total gastrectomy.

It would, therefore, appear that following or in association with a variety of conditions which might conceivably, or which certainly could, in the case of complete gastrectomy, produce a profound disturbance of the secretory activity of the stomach leading to the presence of an achylia, undoubted pernicious anemia has occasionally developed. It is of course possible that this occurrence is merely a coincidence of unrelated diseases, but it is also possible that there is a significant relation. Achlorhydria and even achylia is said to be frequently encountered in cases other than of pernicious anemia, even in normal individuals;[24] and it is apparently true that some cases showing no evidence of pernicious anemia have gastric findings indistinguishable from those invariably found in the patients with fully-developed pernicious anemia. From the work of Bloomfield and of Keefer,[25] however, it is evident that in the majority of instances in the literature the analyses of the stomach contents are not such as would at present be relied upon to exclude the possibility of a secretion of hydrochloric acid under appropriate circumstances. By the use of nonbuffered alcohol test meals, the determination of the actual pH values, and by means of the secretagogue action of the subcutaneous injection of histamin it can readily be demonstrated that many cases showing "no free hydrochloric acid" with older methods will secrete some or even an abundance of acid. Such a result, however, by any method, in cases of Addisonian pernicious anemia is practically unknown. Although it is commonly stated that extensive cancer of the stomach causes an achlorhydria, it is often possible by the use of histamin to develop hydrochloric acid in such cases, and Davidson[10] has used a dye excretion test as a means of distinguishing the achlorhydria of these cases from that of cases of pernicious anemia. It is undoubtedly true, therefore, that the number of cases with "achylia gastrica" which do not have pernicious anemia is less than has been supposed, and, on the other hand,

that the inability of the stomach of the patient with pernicious anemia to secrete hydrochloric acid under any stimulus is profound.

Furthermore, it will be demonstrated in a later paper[26] that the hydrochloric acid alone of the gastric juice has apparently nothing directly to do with the problem of the protection of the individual against a development of the disease. This observation brings into prominence a further defect in the available data, as a result of the failure of most observers to quantitate characteristics of the gastric juice other than its acidity. Although the content of enzyme apparently decreases proportionately to the acid content in most cases, this is not necessarily so particularly, in cases other than of pernicious anemia; and it is a point upon which more actual determinations might be illuminating.

Finally, if for the moment, the cases in which after a complete gastrectomy pernicious anemia has appeared to develop may be interpreted as the result of the operation, it is probable that a time factor of many months is necessary for the development of the disease even in the absence of every bit of functioning gastric tissue. This aspect of the situation has received further emphasis from modern observations of the clinical course of patients with pernicious anemia treated with liver. Those who have continued to ingest adequate amounts of liver have remained well almost without exception,[27] in contrast to the recrudescence of the anemia after varying lengths of time in the cases of a few who have voluntarily discontinued liver therapy. Under these circumstances, the reappearance of the anemia has sometimes been a matter of months.

Evidence as to the Nature of the Disease Inferred from the Effects of Liver Therapy. Strangely enough, it is from experience gained in a study of the patients who have had their blood returned to a normal condition by the use of liver that a fact most suggestive of the possible causal relationship of the achylia to the disease, has been brought out. In these patients, in astonishing contrast to the great improvement of the anemia and other features of the disease, is the total lack of any amelioration of the secretory incapacity of the stomach.[28] These individuals, so clearly and remarkably benefited, nevertheless possess stomachs which seem to be permanently unable to secrete hydrochloric acid; and they must, in order to continue to be well, continue to eat adequately of liver. The converse of this situation is afforded by the case reported by Shaw[29] before the advent of liver therapy. In a man severely ill with pernicious anemia, subsequent to a "spontaneous" remission, free hydrochloric acid was found to have reappeared in the stomach contents of the patient, who was well at last report three years later. If it be supposed that the defective function of the stomach is in some way responsible for the disease, the unusual clinical behavior of Shaw's patient becomes comprehensible, as well as the inevitable tendency of the majority of other cases of pernicious anemia to relapse when liver therapy is discontinued.

A consideration, then, of the facts available from the literature dealing with the subject of the relationship of the achylia to the disease, produces the impression that the contention of a causal relationship is at least a plausible one. Hurst[6] has been the chief exponent in the past of a theory of intestinal sepsis with resulting blood destruction, the abnormal bacterial flora being the result of the absence of the sterilizing action of the acid of the gastric juice. It has been difficult to establish the truth of this hypothesis, and it can now be shown that the intestinal flora are unchanged after the patient has returned to a state of health following the taking of liver.[30] Other theories involving modifications of the conception of intestinal infection have not been proved,[31] and all such hypotheses seem questionable in view of the singularly quantitative nature of the response of the patient to the administration of liver or to a few grams of liver extract daily.

It, therefore, becomes desirable to develop, if possible, a hypothesis which includes the new facts derived from observations with liver therapy, and connects the achylia with the causation of the disease. The quantitative character of the response to liver feeding, both in respect to the regularity of the time of the appearance of the improvement in the blood picture, and in respect to its magnitude, suggests at once the possibility of a dietary deficiency disease. It is in this type of disease that the typical recovery following the supplying of a calculable amount of the factor deficient in the food is so immediately and regularly forthcoming, as, for example, in the relief of experimental scurvy or beriberi in animals. That pernicious anemia can be regularly affected in any way comparable to the effect of the daily administration of 200 to 400 gm. of mammalian liver or kidney, by feeding, in the absence of liver or kidney in the diet, any of the known vitamines has not been demonstrated.[16] Furthermore, with the possible exception of Elders'[33] work there is no evidence known to the author of regularly effective treatment with normal diets or diets containing constituents of the normal diets other than liver or kidneys. Elders has stated that diets rich in vitamins and especially in rare meat will slowly benefit certain patients suffering from sprue or pernicious anemia. The experiments to be described in the present communication do not lend support to these observations. Unless, then, it be supposed that certain articles of the normal diet other than liver or kidneys contain the preventive principle in tangible amounts, presumably equivalent to the dose of liver or kidney necessary to maintain a patient in good health after the relief of the symptoms of fully-developed pernicious anemia, it is difficult to conceive of the disease as due to a simple dietary deficiency comparable, for example, to scurvy. The diet of the unaffected majority of persons in those countries chiefly afflicted with pernicious anemia has contained in the past little or no liver or kidneys; and there are indeed many

healthy individuals who eat little or no animal food. On the contrary, in the patient in whom pernicious anemia has once appeared, the normal diet, if lacking in liver and kidneys, seems to have little or no beneficial effect.

Statement of a Hypothesis Correlating the Achylia Gastrica with the Reaction of the Disease to Liver Therapy. However, it is not difficult to think of a possible connection between, on the one hand, the strongly suggestive evidence yielded by the quantitative nature of the response of the anemia to liver therapy, that pernicious anemia is a dietary deficiency disease, and on the other, the facts, that have been reviewed, suggesting that the achylia gastrica may play a part in the causation of this malady. An obvious possibility is that a virtual dietary deficiency might be produced in the presence of a diet entirely adequate for a normal individual, by the notable defect in the process of gastric digestion necessarily imposed by the absence of functional gastric juice. Since in these patients a lack of hydrochloric acid is almost invariably associated with a corresponding lack of pepsin, the environment for the peptic digestion of protein, which is the chief apparent chemical function of the normal stomach, would appear to be entirely unsuitable. That this reasoning may not be altogether unsound, is further suggested by the statement of Cohn, Minot and their collaborators[16] that the active principle of liver extracts effective in the treatment of pernicious anemia is probably a nitrogenous base or polypeptid and so conceivably a derivative of protein. Means and Richardson[34] have recently considered the possible theories of the nature of the disease with reference to the preliminary report of this paper.

According to this hypothesis, then, the significant defect in the patient with pernicious anemia is an inability to carry out some essential step in the process of gastric digestion, thus causing a lack of whatever substance is successfully derived by the stomach of the normal individual from his food. If this idea were correct, by substituting some digestive process of the normal stomach for the presumably defective mechanism of the patient with pernicious anemia, it might be possible to affect the patient's disease favorably, thus giving evidence of the relief of a deficiency of gastric function. Since the prominent chemical rôle of the stomach in digestion is usually conceded to be a splitting of protein, the effect of the peptic digestion of protein was first undertaken. An account of these preliminary experiments and their results will now be given.

Technique of Observations Designed to Test the Hypothesis of the Achylia Gastrica as a Deficiency Disease-Producing Mechanism. In order to avoid as far as possible the introduction of artificial conditions into the experiments, it was decided as a first observation to carry out the digestion of protein in the stomach of a normal man and to introduce subsequently the products of that activity into the stomach of the patient—*Honi soit qui mal y pense.* Since beef muscle contains about 22 per cent by weight of protein, with only

about 3 per cent of fat and 0.3 per cent of carbohydrate, this substance was selected as a convenient source of protein. It was found possible for a healthy fasting subject to eat 300 gm. of nearly raw finely-ground lean beef muscle (hamburg steak) and after a period of an hour to regurgitate, as a result of pharyngeal stimulation, the entire semiliquid contents of the stomach. To this material was then added enough strong hydrochloric acid to give a pH between 2.5 and 3.5, and the mixture placed in the incubator for periods of time varying from six to thirty hours. In the early experiments, half of the material was incubated for six, and half for thirty hours, the pH being kept on the acid side of 3.5 by appropriate additions of strong hydrochloric acid. After incubation, the fully liquefied material was passed through a fine sieve and neutralized to a pH of about 5 with strong sodium hydroxide, and at once introduced into the stomach of the patient by means of a Rehfuss tube. In order to complicate the experiments as little as possible by other digestive action, the material was given in the evening after the patient had fasted for at least six hours, and no food was eaten until an hour after the feeding. The patients were kept on a diet containing no meat, liver or kidneys, but were allowed eggs for breakfast and chicken and fish occasionally.

Radiographic studies of mixtures of barium sulphate with the hamburg-steak meals showed that in the subjects who furnished the normal gastric digestion, about one-third of the meal passed beyond the pylorus within the hour. The material as recovered after vomiting, thus representing the products of the normal gastric digestion of about 200 gm. of beef muscle, was semiliquid, reddish-brown, contained a good deal of mucus, and had an acidity usually in the vicinity of pH 4 to 5. On rare occasions a slight amount of bile was regurgitated. Bacteriologic studies after the incubation period showed a very slight growth of bacteria. A microscopic growth of yeasts and molds occasionally appeared during the longer periods of incubation of the material. Care was exercised that all subjects, who were healthy medical students or physicians, were free from upper respiratory infections. In a few instances, when initiating the procedure, the mere bulk of the material resulted in mild gastric distress and occasionally in vomiting of portions of the predigested material. On the contrary, the relief of persistent nausea or diarrhea was occasionally surprisingly effected by a single administration of this material.

The patients studied in these series of experiments were all undoubted cases of the classical Addisonian pernicious anemia as evidenced by the finding in all of a characteristic blood picture, a complete absence of free hydrochloric acid in the gastric contents, and in most, a glossitis, gastrointestinal or neurologic symptoms. The initial red blood-cell counts varied from 750,000 to 2,700,000 per c.mm., and no patient was utilized whose condition would not warrant the administration for at least ten days of a potentially

negative material. It was at once discovered that as objective evidence of the effectiveness of the material given, could be taken the changes in the blood associated with the feeding of liver and liver extracts described by Minot and his associates[35,36] namely, a prompt, transient increase of the number of immature red blood cells in the peripheral blood stream followed by a progressive increase of the red blood cell-count. Following the administration of effective doses of liver to pernicious anemia patients these authors have shown that, usually before the seventh day of the treatment,

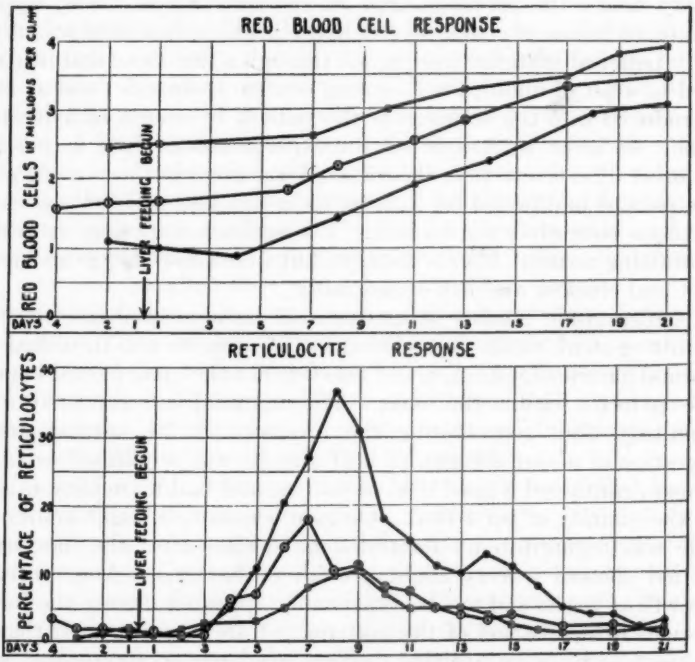

FIG. 1.—The effect on the reticulocytes in pernicious anemia of feeding daily 220 gm. of liver pulp to each of 3 patients with different red blood-cell levels. The same type of line in each part of the figure records data for the same patient. In general, the highest blood-cell count is accompanied by the lowest reticulocyte count and *vice versa*. (Minot, Murphy and Stetson.)[35]

the percentage of reticulocytes (reticulated red blood cells in films vitally stained with brilliant cresyl blue), shows an increase. This percentage progresses to a maximum within a few days and then decreases to approximately the initial value within three weeks. During this period there is a progressive increase of the total red blood-cell count which is at first due entirely to the increment of reticulocytes, but later is the result of new cells without reticulation delivered to the blood stream. A typical illustration of the effect of liver feeding on adult and reticulated red blood-cell values may be

seen in Fig. 2. Smaller but effective amounts of liver will produce a reticulocyte response which does not attain such a large maximum and which may be more prolonged. Indeed, the increase of reticulocytes is a far more sensitive index of improvement than the increase of the total red blood-cell count, since it is possible for the former to appear transiently in response to a feebly potent substance, without any effect on the red blood-cell count whatever being observed. Yet, if any material in uniform daily dosage is effective it is the rule to attain the maximum increase in the reticulocyte percentage usually before the tenth, certainly before the fourteenth day of the therapy. The reticulocyte response is also roughly inversely proportional to the number of red blood cells, as shown in Fig. 1, in patients with

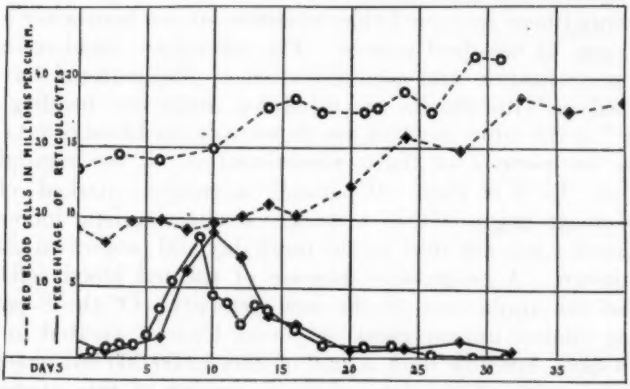

FIG. 2.—The effect on a case of pernicious anemia (Case 1) of the daily administration of the contents of the normal human stomach recovered after the ingestion of 300 gm. of beef muscle is compared with the effect on a similar case of the daily ingestion of moderate amounts of liver. The reticulocyte (solid lines) and adult red cell (broken lines) values of Case 1 (represented by diamonds) are compared with those of the similar case (represented by circles). The reticulocyte responses of both patients are chronologically similar, although the number of reticulocytes produced in Case 1 by the gastric contents is not as great relative to the lower initial red blood-cell count of this patient compared to that of the other patient. An increase of over 1,000,000 red blood cells per c.mm. was observed to take place within thirty days in Case 1.

counts under 3,000,000 per c.mm. Because of the repeatedly demonstrated time relations of this quantitative increase of young red blood cells with successful liver therapy, it may be confidently used to test within a few days the therapeutic properties of any substance, and for that reason has been employed in these experiments. Furthermore, the failure of this reaction to appear within ten days may be taken as evidence of the ineffectiveness of the material given. As additional proof that the patients, who form the basis of these observations, were in truth cases of Addisonian pernicious anemia, may be cited the fact that this characteristic reaction was obtained either with a test substance or later with liver or liver extract of known potency, in every one of the patients.

All blood counts were made from exactly 5 cc. of blood drawn from the arm veins without stasis, and rendered incoagulable by the addition of a drop of a saturated solution of potassium oxalate. As the small dilution factor was invariable no account of it was taken. The vital stains for reticulocytes were made either from the recently drawn oxalated blood after shaking or from a drop of capillary blood. The percentage of these reticulocytes was estimated by counting 500 or 1000 cells, and the maximum percentages were usually checked by another observer.

The Effect of the Administration of the Contents of the Normal Human Stomach Recovered after the Ingestion of Beef Muscle. The observations now to be described were made on 10 patients, the entire number of those to whom were given daily the gastric contents of a normal man recovered three-quarters to one hour after a meal of 300 gm. of rare beef muscle. The subsequent incubation with acid, neutralization and administration of this material has been described and the results are tabulated under the heading "test periods" in the table, in which are shown only the blood counts made during the periods of daily administration of the regurgitated material. In 8 of these 10 patients so treated, marked clinical improvement began within a week. A characteristic increase of reticulocytes was manifest by the tenth day and progressed through a maximum. A progressive increase of the red blood cells then followed the appearance of the new elements. Of the 8 patients showing clinical improvement only one, Case 4, treated for only sixteen days, failed to show a gain of over 1,000,000 red blood cells per c.mm. within forty days of the beginning of this manœuvre. Three of the 8 cases, 1, 2 and 3, showed a gain of 2,000,000 red blood cells in that time. As in the response to liver therapy, the patients with the lower initial red blood-cell counts show the higher maxima of reticulated red blood cells. As an actual basis of comparison, in Fig. 2 is shown the response of the reticulated and adult red blood cells in Case 1 on the same chart with these data derived from a case with a similar initial red blood-cell count, which was treated with moderate daily doses of liver. It will be seen at once that the reactions of both patients are similar.

An inspection, then, of the results set forth in the table shows clearly that a response occurred in 8 of the 10 patients, and was entirely comparable to what might have been expected with moderate uniform daily doses of liver. In 1 of the 8 cases benefited, Case 4, the effect might have been initiated by a coincident transfusion, but the reticulocyte reaction of the patient is quite comparable to that of the other 7, although the discontinuation of the effective material occurred before any increase of the red blood-cell count had appeared. Two of these cases, 5 and 7, showed no perceptible clinical improvement, although in Case 5 at the expected time there was a slight increase of the reticulocytes. These 2 cases, together with Case 6, were treated with material which was transported to another city

TABLE GIVING RESULTS OF ADMINISTERING CONTENTS OF NORMAL HUMAN STOMACH RECOVERED AFTER INGESTION OF BEEF MUSCLE TO 10 CASES OF PERNICIOUS ANEMIA.

CONTROL PERIODS.

(Daily administration of various substances as indicated below.)

Days of treatment.	Beef muscle, 200 gm.		Beef muscle, 250 gm.		Beef muscle, 300 gm.		Stomach contents at pH 2.5.		Stomach contents, heated 80° C.		Meat-free diet.		No control.		No control.		Stomach contents, chy. meal.		Beef muscle, pig's stomach, each 200 gm.	
	Case 1. R.B.C. (mils.).	Retics. (%).	Case 4. R.B.C. (mils.).	Retics. (%).	Case 10. R.B.C. (mils.).	Retics. (%).	Case 2. R.B.C. (mils.).	Retics. (%).	Case 6. R.B.C. (mils.).	Retics. (%).	Case 8. R.B.C. (mils.).	Retics. (%).	Case 3. R.B.C. (mils.).	Retics. (%).	Case 9. R.B.C. (mils.).	Retics. (%).	Case 5. R.B.C. (mils.).	Retics. (%).	Case 7. R.B.C. (mils.).	Retics. (%).
0 . .	1.86	1.1	....		2.68		1.03	3.8	1.11	0.4	2.76	1.0	....		....		1.54	0.4	1.41	2.4
2 . .	1.89	1.5	0.95	2.1	2.62	1.9	0.75	2.5	1.13	0.5	2.76	0.4	....		....		1.52	0.3	1.63	2.2
4 . .	2.20	1.5	0.96	3.8	2.58	2.0	1.07	1.6	1.19	2.2	2.70	0.4	....		....		1.55	0.3	1.58	1.6
6 . .	2.41	1.7	0.96	2.8	2.24	1.6	0.75	4.6		4.0	2.70	0.3	....		....		1.48	0.2		1.5
8 . .	1.86	0.8	0.94	2.4	2.36	0.8	0.64	3.2	1.08	2.0	....		....		....		1.47	0.2	1.33	1.2
10 . .	1.88	1.1	Transfusion		2.36	2.0	0.84	3.2	....		2.77	0.5	....		....		1.38	0.1	1.41	0.4

TEST PERIODS.

(Daily administration of contents of normal stomach recovered after ingestion of 300 gm. of beef muscle.)

2 . .	1.66	0.5	1.87	1.0	2.61	0.2	0.65	3.4	1.19	2.0	2.77	0.5	2.36	0.4	1.57	0.8	1.44	0.1	1.29	1.0
4 . .	1.96	1.1	1.80	0.8	2.56	0.6	0.80	9.8	1.25	1.4	2.88	1.4	2.60	0.8	1.68	0.6	1.48	0.6	1.12	1.2
6 . .	1.98	1.6	1.37	0.3	2.48	0.8	0.86	6.6	1.26	9.6	2.95	0.8	2.46	4.8	1.24	0.7	1.56	0.6	1.48	2.2
8 . .	1.81	6.4	1.52	6.5	2.52	2.8	0.89	**16.0**	1.42	**11.6**	3.19	0.6	3.40	**7.8**	1.33	0.9	1.65	2.1	1.24	3.2
10 . .	1.92	**9.0**	1.50	10.3	2.68	**6.8**	1.10	15.0	1.41	7.8	3.21	**1.8**	3.20	5.5	1.66	4.6		2.5	0.86	1.6
12 . .	2.01	7.2	1.72	**16.9**	2.69	5.5	1.44	7.4		7.0	3.24	1.6	3.47	3.6	1.53	9.6	1.42	**4.1**	1.07	0.6
14 . .	2.22	3.1	2.05	7.4	3.00	4.0	1.48	5.1	1.48	5.2	3.34	0.2	3.57	7.5	1.39	**13.2**	1.48	3.5		
16 . .	2.06	2.4	1.84	3.2	3.00	2.6	1.71	5.0	1.62	4.2	3.18	1.2	3.73	6.4	1.55	8.4	1.22	2.8		
20 . .	2.54	0.7	....		3.58	1.0	1.87	4.8	1.69	5.4	3.21	0.2	4.05	3.3	1.46	8.8				
24 . .	3.16	0.8	....		....		2.54	2.4	2.20	1.2	3.64	0.5	4.57	2.6	1.84	3.6				
28 . .	2.92	1.4	....		....		2.85	1.3	2.53	0.7	3.72	0.4	....		2.21	4.2				
32 . .	3.73	0.4	....		....		2.66	0.2	2.42	0.8	3.50	0.4	....		2.63	7.6				
36 . .	3.50		....		....		3.05	0.3	2.67	1.6	3.48	0.6	....		2.71	5 6				
40 . .	3.66		....		....		3.22	0.3	2.85	0.5	3.88									

following neutralization with sodium hydroxide. The prolonged delay, sometimes as much as twenty hours, before this material could be given to the patients, may have conditioned these two failures, possibly by affording an opportunity for bacterial growth. That these two refractory cases were true cases of pernicious anemia was proved by their entirely typical subsequent reaction to liver extract.

The Effect of the Administration of Beef Muscle. Elders[33] has stated that, apparently without liver or kidneys, high meat diets with ample vitamins will slowly improve patients suffering from sprue or pernicious anemia. It was considered theoretically possible that muscle, being of animal origin, might contain, as does liver or kidney, a certain amount of the effective principle. In order to ascertain whether the effect seen in the first group of patients was not simply due to the ingestion of substances already present in the meat before it was introduced into the normal stomach, the following observations were made. Considering that the purely physical effects of fine division involved in the predigestion of the meat might make more available to the patient's use some substance already present, to three of the patients in the first group just described were given daily 200 or more grams of lean beef muscle at pH 5. This meat was as finely divided as possible by passing it through a special meat chopper used in the preparation of liver pulp, or by passing it three times through the usual "Universal" type machine with a fine cutter. It was then mixed with enough water to give it a semiliquid consistency, giving a product of approximately pH 5. This material prepared from 200 gm. of beef muscle was given daily to Case 1 in divided dosage between meals. In a similar fashion Case 4 took 250 gm. daily, and Case 10, 300 gm. of beef muscle daily prepared in the same way. Clinically these cases were not only not improved but said they felt progressively worse. Case 4 suffered from loss of appetite and had some diarrhea despite frequent doses of paregoric. An inspection of the data given in the table under the heading "control periods" shows that there was no significant change in either reticulocytes or total red blood cells; certainly nothing in any fashion comparable to the effect of the administration of similar or smaller amounts of beef muscle given daily in subsequent "test periods" to the same patients after the beef muscle had been received into and recovered from the stomachs of normal fasting men.

It may be objected, however, that the "control periods," being only ten days in length, are not sufficiently long to test the possible low potency of the meat. In these experiments, however, it is the difference between the test and the control periods which it is desirable to observe; and in the experience of Minot[35] and others, the first four days of any ten-day period give ordinarily, even while an effective liver extract is being administered, no evidence of its activity, but must be considered as a continuation of the effect of

any immediately preceding test period of ten days. In these 3 cases, then, the first four days of the "test period" immediately succeeding the "control period" likewise evidence no changes in the reticulocytes and hence give a period of days sufficient to give assurance of the essential inability of lean meat alone to confer any benefit under these conditions. It is to be remembered, however, that it cannot be assumed from these observations that such a diet carried on for months might not be in some way very slowly beneficial as Elders has claimed.[33] These experiments, however, lend no confirmation to his statements, and certainly give evidence that there is no substance already present in raw lean meat which can give effects comparable to those demonstrable in a subsequent period with that amount of meat after a sojourn in the normal stomach. This effect, therefore, necessarily suggests a significant difference between the action of the stomach of the patient and that of the normal man.

Discussion. The foregoing experiments clearly demonstrate that the stomach contents of a normal man recovered during the digestion of a meal of beef muscle and subsequently incubated with additional hydrochloric acid contain a substance capable of causing remissions in certain cases of pernicious anemia comparable to those produced by moderate amounts of liver. It was also shown that beef muscle given directly to these same patients had no effect under the conditions of these experiments. This certainly means that no preformed constituent of the beef muscle could have been the basis of the effect seen after recovery of the beef muscle from the normal stomach, and implies either the direct action of some constituent of the secretions produced by the normal man or some action of these secretions on the meat.

The original hypothesis as to the nature of the disease, of course, necessitates for its proof the demonstration of an action of the gastric juice on the food. The foregoing experiments do not afford a basis of discrimination between these two possibilities, since the observations are consistent with either a direct activity of the normal gastric juice or its indirect action on the beef muscle to produce activity. Because both the highly cellular liver and kidney of the healthy animal are known to contain a water-soluble substance effective in the treatment of pernicious anemia, it appeared quite possible that the secretion of the cell-filled mucosa of the stomach might contain a plentiful amount of a similar soluble and effective constituent, obtained incidentally in the gastric juice recovered from the normal stomach with the beef muscle. If this were true the experimental evidence could not then be used to support very strongly the idea of a unique capacity of the normal stomach to produce in some way from the food of the normal man his supply of preventive substance for pernicious anemia. In the event of a subsequent demonstration of the effectiveness of gastric juice alone, it could only be suggested that the stomach alone of all the organs of the body could secrete a substance perhaps later stored in the

liver or kidney, since this demonstration would, of course, give no proof of the stomach as the original source of the effective substance. On the other hand, if it could be shown that the gastric secretions themselves were ineffective unless allowed to come into contact with the beef muscle, clear evidence of a method of producing a preventive substance from an external source would be at hand, and a step taken toward the proof of the original hypothesis as to the mechanism of the disease. Experiments upon this point are reported in the following article of this series.[26]

The demonstration of the ineffectiveness of finely-divided beef muscle itself in causing remissions does more than eliminate the muscle as a source of the substance causing the effects. It bespeaks an important difference between the stomach of the patient and of the normal man, suggesting that it is possible for the latter to respond in some way to the presence of the beef muscle with the production of an effective substance. The stomach contents of the patient, on the other hand, are thus shown not to contain in the presence of the beef muscle a detectable amount of the effective substance, which can apparently be produced in considerable amounts by the normal man under these circumstances and made available to the patient by transference to his stomach. Again, however, it is apparent that the significance of this negative demonstration depends mainly on whether it can be shown that the positive ability of the normal stomach depends on an action of gastric juice upon the beef muscle and not on a direct action of the gastric juice itself.

Summary and Conclusions. 1. A consideration of the existing facts concerning the achylia gastrica of Addisonian pernicious anemia, together with the recently acquired knowledge of the effects of liver therapy, leads to the conception of the disease as possibly due to a deficiency of a new type.

2. A working hypothesis has been developed which postulates that the development of the disease is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the face of a diet adequate for the normal man.

3. The results of observations designed as a preliminary test of this hypothesis are reported and are believed to be consistent with it but not necessarily to prove it.

(*a*) To each of 3 cases of pernicious anemia was given daily for a period of ten days between 200 and 300 gm. of finely-divided raw beef muscle without demonstrable effect on the blood formation during a total of fourteen days.

(*b*) Immediately thereafter to each of these 3 patients and to 7 others were given daily the incubated contents of a normal human stomach recovered after the ingestion of similar quantities of beef muscle. In the 3 patients mentioned, and in 5 of the 7 others, comprising in all 10 patients so treated, there appeared before the tenth day an increase of the immature red blood cells followed by a

progressive improvement of the anemia entirely similar to that ordinarily observed with the daily ingestion of moderate amounts of liver by similar patients.

4. It is concluded, therefore, that in contrast to the conditions within the stomach of the pernicious anemia patient, there is found within the normal stomach during the digestion of beef muscle some substance capable of promptly and markedly relieving the anemia of these patients.

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OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA

II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle after Incubation with Normal Human Gastric Juice.*

By William B. Castle, M.D.,

Instructor in Medicine, Harvard Medical School, and Associate Physician, Thorndike Memorial Laboratory, Boston City Hospital,

and

Wilmot C. Townsend, M.D.,

Assistant in Tropical Medicine, Harvard Medical School; Assistant Resident Physician, Thorndike Memorial Laboratory, and Resident Physician, Tropical Medical Service, Boston City Hospital.

(From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine of the Harvard Medical School, Boston, Mass.)†

It has already been demonstrated that in the incubated contents of the normal human stomach removed during the process of

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digestion of beef muscle there is present a substance which is similar to mammalian liver or kidney in its ability to produce remissions in the disease pernicious anemia.[1] It has also been shown that beef muscle fed as such to pernicious anemia patients did not produce such an effect. These observations were considered to be consistent with, but not proof of, the hypothesis that the obviously defective peptic digestion of the patient with pernicious anemia might be the basis of a virtual dietary deficiency in the presence of a diet adequate for the normal man.

There are, however, two general ways in which these results may be explained quite consistently with the recognized physiologic differences between the stomachs of the patients and those of normal individuals: (1) it is possible that some substance present in the secretions of the normal stomach, quite independently of the ingested beef muscle, might be the basis of the effects observed. The hydrochloric acid and the pepsin of the normal gastric juice are the chief substances found lacking in the stomach of the patient with pernicious anemia; but the cell-rich mucosa of the normal stomach might be, like the highly cellular mammalian liver, the source of a water-soluble extract secreted in the gastric juice and possessing properties similar to those that may be readily prepared from liver;[2] (2) however, the possibility exists, which is consistent with the original hypothesis, that gastric juice to produce these effects must in some way act upon the beef muscle.

An additional step toward the proof of the original hypothesis would then be taken, provided the first of these alternatives could be eliminated. If it could be shown that gastric juice secreted in the absence of beef muscle or other food is inactive, but that on being brought into contact with beef muscle, itself already shown to be inert, a potent substance was produced, the original hypothesis would be further substantiated. Experiments designed to test this possibility will now be described.

The Effect of the Administration of Human Gastric Juice Alone and after Incubation in Vitro with Beef Muscle in the Presence of Hydrochloric Acid. A solution of the problem of securing adequate amounts of fresh active human gastric juice secreted entirely apart from any food substance was found with the use of subcutaneous injections of histamin phosphate.[3] The normal fasting subject was injected with a dose of histamin phosphate in sterile salt of between 0.5 and 0.75 mg. By means of a Rehfuss tube and syringe the gastric juice was removed as fast as secreted for a half hour, following which another injection of histamin was given and the gastric juice collected for another half hour. The average subject under these conditions secreted abut 150 cc. of a colorless, or occasionally somewhat bile-tinged liquid containing some mucus. This fluid was then filtered through compress cloth and kept in the ice box until needed. The juice was active proteolytically, and had a free hydro-

TABLE GIVING RESULTS OF ADMINISTERING BEEF MUSCLE AFTER INCUBATION WITH NORMAL HUMAN GASTRIC JUICE TO 10 CASES OF PERNICIOUS ANEMIA.

CONTROL PERIODS.

Daily administration of various substances as indicated below.

Days of treatment.	Gastric juice, 300 cc.		Gastric juice, 150 cc.; casein.		Gastric juice, 150 cc.; muscle prot.		No control.		Spleen pulp, 200 gm.		Beef muscle, 200 gm., incubated with HCl*—administered during morning. Gastric juice, 300 cc., incubated with HCl —administered during afternoon.									
	Case 11.		Case 19.		Case 24.		Case 14.		Case 18.		Case 17.		Case 15.		Case 16.		Case 13.		Case 12.	
	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).
0	1.37	0.4	0.70	5.0	1.78	2.8	....		1.30	2.1	1.30	0.4	1.88	1.0	1.68	2.6	1.66	1.2	1.94	0.6
2	1.38	2.4	0.74	2.8	1.37	2.6	....		1.14	2.0	..	0.2	2.07	1.6	..	4.6	1.74	1.8	2.06	1.4
4	1.36	2.8	0.75	3.1	1.39	3.0	....		1.21	1.5	1.74	0.2	2.04	2.7	1.51	2.8	2.16	2.0	1.74	0.4
6	1.37	2.0	0.77	1.6	1.45	2.6	....		1.25	1.0	1.48	1.4	1.80	4.0	1.47	4.0	1.72	1.8	1.70	0.2
8	1.60	2.1	0.76	1.4	1.62	2.1	....		1.23	1.0	1.71	0.4	1.76	3.4	1.45	7.0	1.39	2.0	1.66	0.2
10	1.48	1.2	....		1.36	1.2	....		1.21	0.5	1.53	0.6	2.29	4.0	1.52	6.2	1.38	2.4	1.68	0.4
12	....		....		....		....		....		....		....		1.70	**15.6**				

TEST PERIODS.

Daily administration of 200 gm. of beef muscle after incubation with 300 cc. of gastric juice.

2	1.38	1.4	0.74	1.8	1.53	1.2	1.28	0.4	1.45	0.1	1.52	0.6	2.12	2.4	2.09	7.8	1.32	2.6	1.45	0.6
4	1.43	2.0	0.82	4.4	1.17	2.8	1.30	1.2	1.30	0.9	1.41	1.8	2.20	2.7	2.13	6.4	1.23	1.8	1.46	1.4
6	1.66	6.4	0.80	9.3	1.48	7.8	1.70	8.4	1.34	8.0	1.57	2.8	2.15	3.9	1.94	9.5	1.30	3.4	1.41	1.6
8	1.73	**11.4**	1.22	18.4	1.64	**13.0**	2.02	**16.0**	2.06	**14.0**	1.22	8.4	2.39	**8.6**	2.20	**12.8**	1.48	**5.2**	1.24	1.2
10	2.01	7.4	1.22	**30.2**	1.75	8.8	2.15	7.6	..	3.5	1.92	11.0	2.57	5.9	2.21	12.3	1.50	3.6		
12	2.29	4.8	1.71	12.2	1.86	9.4	2.22	4.8	2.30	2.0	2.04	**15.2**	2.94	3.0	2.58	7.2	1.47	2.0		
14	2.23	3.6	1.87	2.6	2.18	7.9	2.68	3.0	2.49	0.8	2.32	10.4	2.59	3.8	2.53	5.0	1.40	1.0		
16	2.57	2.4	2.07	1.2	2.26	5.0	2.68	1.6	3.10	0.5	2.59	5.0	3.03	2.6	2.70	3.2				
18	2.64	2.2	2.08	2.6	2.36	1.2	....		2.90	0.3	2.63	2.4	..	1.2	2.65	3.2				
20	....		2.43	1.0	2.54	2.2	....		2.98	0.3	2.68	1.8	3.10	1.4	3.11	1.4	Subsequent poor response to liver extract; both cases had cystitis.			
22	....		....		....		....		....		3.08	1.2	3.20	1.4	....					
24	....		....		....		....		....		....		....		....					
26	....		....		....		....		....		....		3.58	1.0	....					

* The beef muscle was incubated with water instead of hydrochloric acid in Cases 12, 13 and 15.

chloric acid content of from 40 to 50 cc. of tenth normal hydrochloric acid, with a total acid content of about 10 cc. more of tenth normal hydrochloric acid per 100 cc. of gastric juice. In the experiments to be described, the daily contribution of one or two individuals collecting gastric juice for one hour was used each day in the treatment of each patient. The 10 patients comprising this group were all clinically cases of Addisonian pernicious anemia by the criteria mentioned in the preceding paper.[1] The studies of the blood were conducted as therein described, and the effectiveness of the substances administered was judged on the basis of the response of the reticulocytes and total red blood-cell values[4] as discussed in the same paper. In the table are shown the results of the experiments on the 10 patients of this group.

It was desired first to test the effect of gastric juice alone. Accordingly, to Case 11 was given in the control period a daily average of about 300 cc. of the pure gastric juice. An inspection of the reticulocyte data during this ten-day period shows no significant change and the red blood-cell count remained essentially stationary. The patient said that he felt a little better toward the end of the observation and seemed perhaps to have a slightly better color, but in the next four days no new cells appeared in the blood films. We may then fairly conclude that in this patient 300 cc. of the gastric juice given daily for ten days was virtually ineffective.

The procedure in this case was now changed so that every day 200 gm. of finely divided beef muscle, after thorough admixture with 300 cc. of gastric juice from the same normal subjects, was incubated at 37° C. in a glass beaker with occasional stirring for a period of two hours. The acidity of the mixture was maintained at a pH between 2.5 and 3.5 by sufficient additions of strong hydrochloric acid. At the end of this incubation period the liquefied contents of the beaker were passed through a fine wire sieve, neutralized with strong sodium hydroxide to pH 5, and given without inconvenience by a Levin gastric tube to the fasting patient. It is to be noted that the methods of this incubation *in vitro* with fresh gastric juice are identical with those employed in the *in vitro* phase of the digestion of the regurgitated beef muscle.[1] In marked contrast to the negative results just obtained in this patient with pure gastric juice alone was the striking effect of the incubation of the gastric juice with the beef muscle. There followed prompt clinical improvement and an appearance of reticulocytes in the peripheral blood stream, reaching a maximum of 11.4 per cent on the seventh day of this treatment. There was a progressive increase of the patient's red blood-cell count from 1,376,000 to 2,640,000 per c.mm. in a period of eighteen days.

This experiment is confirmed in its essentials by the observations on Cases 19 and 24. In the control periods of these 2 cases 150 to 200 cc. of gastric juice secreted after histamin were incubated re-

spectively with commercial casein and with a protein prepared from beef muscle after solution of the muscle in strong sodium hydroxide. The products of these incubations did not produce a remission as is now known because of the improper nature of the protein used; but the evidence is presumptive that the gastric juice employed would have been similarly ineffective alone. In the subsequent test periods of these 2 cases, incubations of similar quantities of gastric juice with 200 gm. of beef muscle produced reticulocyte maxima of 30.2 and 13 per cent respectively, as quantitative evidence of the remissions obtained. In Case 24 an increase of from 1.53 million to 2.54 million, and in Case 19 an increase of from 0.74 million to 2.43 million red blood cells per c.mm. were observed to take place in twenty days.

These three experiments strongly suggested that some action of human gastric juice was capable of producing from 200 gm. of beef muscle, known itself to be without effect,[1] a substance capable of causing a remission in pernicious anemia quite comparable to the action of 150 gm. of prepared liver. There still remained, however, the possibility that the combination of gastric juice and beef muscle was effective, not from any essential mutual interaction, but merely from a summation of substances already present in each separately. Even if each contributed a subliminal quantity, together they might, without interaction of any sort, contain initially a total amount of effective substance sufficiently great to be detected. Such might even conceivably be the cause of the remissions seen when the two substances were recovered, necessarily together, from the normal human stomach during the digestion of the meat or after incubation together *in vitro*. Accordingly, further experiments were undertaken in order to settle this point and to confirm if possible the positive results of the *in vitro* incubation of the beef muscle with gastric juice as described in the treatment of Cases 11, 19 and 24.

It was desired to give in a control period to the patients separately the same amounts of the two individually ineffective constituents of the combination, which after incubation together *in vitro* had been found effective. In order to reproduce as far as possible the conditions existing during the incubation of a mixture of the gastric juice with the beef muscle in the presence of hydrochloric acid, to be carried out in the subsequent test periods, each of the materials was to be incubated *separately* for two hours in the presence of hydrochloric acid and then neutralized with strong sodium hydroxide to pH 5 just before administration to the patient at *separate times*. The natural reaction of the hydrochloric acid content of the gastric juice, usually between pH 1 and 2, was the acidity of the incubation period of this substance. In the management of Cases 16 and 17 sufficient dilute hydrochloric acid was added to the finely ground beef muscle to give a pH of between 2.5 and 3.5; in Cases 12, 13 and 15, the beef muscle was merely suspended in water during the

incubation period at pH 5. In order to give separately during the control period the same amounts of the two substances, gastric juice and beef muscle, that were to be given during the test period after incubation together, each patient received daily for at least ten days during the late afternoon and evening 250 to 300 cc. of the incubated gastric juice prepared as above described, and during the morning and early afternoon 200 gm. of the finely ground incubated beef muscle.

In the test periods immediately subsequent to these control periods similar quantities of pure gastric juice, usually from the same subjects were thoroughly mixed with 200 gm. of beef muscle and the material placed in the incubator. There it was allowed to remain for two hours with occasional stirring, at an acidity of pH 2.5 to 3.5, maintained by appropriate additions of strong hydrochloric acid. At the end of this incubation period, the liquefied contents of the beaker were passed through a fine wire sieve, neutralized with strong sodium hydroxide to pH 5, and given by Rehfuss tube to the fasting patient. It will be noted that this procedure is identical with that already described for Cases 11, 19 and 24 during the test periods.

The total quantity of both the gastric juice and beef muscle taken by these five patients during any day or given number of days of both the control and the test periods was therefore identical; and the conditions of incubation as far as possible were the same except for a slightly more acid reaction of the separately incubated gastric juice and except for the omission of the hydrochloric acid in the separate incubation of the beef muscle during control periods of Cases 12, 13 and 15. The significant difference between the two periods was, however, that during the control period these two substances were *incubated and administered separately* to the patient, but *incubated together and necessarily so administered* during the subsequent test period. *Therefore, any differences between the action of the patients during the control and test periods must necessarily be due to the effects of the interaction of the two substances: gastric juice and beef muscle.*

The complete data from all blood examinations made while the 5 patients of this special group were the subjects of the experimental procedures are presented in the table. It will be seen there that Cases 12, 13 and 17 showed during the control period no evidence of a significant increase of reticulocytes. There was no evidence of an increase of the red blood-cell count and no detectable clinical improvement in these patients. In fact, in Cases 12 and 13, there was a distinct increase of the anemia together with other symptoms. The condition of these two female patients was unfortunately complicated by the presence of a cystitis. In the case of Patient 12 the clinical condition did not improve in the test period; and during the test period of Case 13 there was a slight but perceptible rise of

the reticulocytes to a maximum percentage of 5.2 on the seventh and eighth days. There was with this no increase of the red blood-cell count during fourteen days—a result which may be obtained with small reticulocyte increases due to liver extract of low potency.[4] It became obvious, however, when after only a few days of the test periods had been completed and it appeared advisable to begin treatment with liver extract, that these 2 patients, presumably from the effects of the complicating cystitis, could not react satisfactorily even to maximum dosage with liver extract known to be effective. The refractory character of Case 12 was thus clearly demonstrated, and the poor response of Case 13 in the test period was explained. Unfortunately, nothing as to the relative potency of the materials administered in the control and test periods of Case 12 can be inferred.

An inspection of the data compiled from Case 17, however, leaves no doubt of the significance of the interaction of the gastric juice and beef muscle during their incubation *in vitro* in reproducing the effects already seen in the test periods of Cases 11, 13, 19 and 24. On the contrary, during the ten-day control period there was not the slightest evidence of clinical improvement in this patient. The red blood-cell count remained stationary and the reticulocyte percentage showed no significant change, even though the patient was daily ingesting *separately* 200 gm. of beef muscle previously incubated for two hours with hydrochloric acid, and between 250 and 300 cc. of similarly incubated fresh human gastric juice. A few days after this patient began to be given daily the same quantity of these substances incubated *together* in the presence of hydrochloric acid, however, subjective improvement was noted. An increase of reticulated red blood cells appeared in the circulating blood on the fifth day of this regimen and reached a maximum of 15.2 per cent on the twelfth day. During the twenty-two days of this treatment the red blood-cell count rose from 1.52 to 3.08 million per c.mm., and there was a corresponding increase of the patient's color, appetite and activity. Quite of this nature was the clinical improvement seen during the test periods of the other cases of this type, Cases 15 and 16. As will be seen by inspection of the table, these patients showed during the test periods ample evidence of the objective changes in the reticulocyte and total adult red-cell counts which are seen with liver feeding in moderate amounts.[5] In both instances a gain of 1,000,000 red blood cells per c.mm. was produced within twenty-one days by the material digested *in vitro*.

In the control periods of these 2 cases, 15 and 16, a repetition of the negative results of the control period of Case 17 is not seen. There is in the reticulocyte data of Case 15 evidence of a very slight rise; and in Case 16 a pronounced rise to as high as 15.6 per cent appeared on the thirteenth day of this prolonged control period. However, in the subsequent test periods, it became obvious that the beef

muscle and gastric juice after incubation together were distinctly more effective than these constituents of the test material given as far as possible separately. Case 15 attained a subsequent maximum reticulocyte percentage of 8.6 even at a red blood-cell level at which only slightly over 10 per cent was to be expected with the extract from 400 gm. of liver daily.[4] Patient 16 also showed a second reticulocyte rise during the test period. This phenomenon is characteristically encountered, according to Minot,[5] if the uniform daily administration of an effective liver preparation is followed at a short interval by a uniform daily administration of a larger dose of the same, or a similar amount of a more potent material. Here it may be confidently regarded, by analogy with the same phenomenon in observations on cases treated with liver extracts, as indicative that the effectiveness of the material administered in the test periods of these cases was greater than that given in the control periods.

Although it cannot be stated with certainty that the beef muscle and gastric juice would both invariably be inactive under the conditions of the control periods of these experiments, if it were possible entirely to exclude the chance of contact between these two substances within the patient, nevertheless this appeared to be the case in the control periods of Patients 17 and 13. In Case 15 the evidence of an effect during the control period is tenuous, but in Case 16 there was an undoubted effect. A consideration of the experimental conditions necessarily imposed by such conduct of the control periods as was here carried out, suggests at once an explanation for these variations. It was of course possible to be certain of the complete lack of contact between the beef muscle and the gastric juice only up to the moment of administration to the patient. Although given at times as widely separated during any one day as was reasonably possible, there still existed a definite chance for interaction between these substances in some portion of the gastrointestinal tract of the patient. It was hoped that the combined incubation of the test periods would provide a sufficiently great opportunity for interaction in contrast to the absence of any such contact *in vitro* in the control observations, so that a difference amounting even possibly to an absence of an effect in the control periods would be observed. This was realized in 2 patients, 13 and 17; and in the other 2 cases reacting in the test period clear evidence of an effect greater than that seen in the preceding control period was observed.

In further confirmation of the regularity with which the incubation of gastric juice has been found to produce an effective substance from beef muscle, are presented in the table the data from 2 more cases, 14 and 18. Case 14 had no control period but showed in the test period a maximum reticulocyte production of 16 per cent on the eighth day, and an increase of the total number of red blood cells from 1.28 to 2.68 million per c.mm. in 16 days. Case 18 was given 200 gm. of raw spleen pulp daily without effect during the ten days preceding

the test period. In the test period an excellent remission appeared as a result of the administration of the products of the incubation of the beef muscle with gastric juice. A maximum figure of 14 per cent of reticulocytes appeared on the eighth day with an increase of the total red blood-cell count from 1.45 to 2.98 million per c.mm. in twenty days.

Of this group of 10 cases of pernicious anemia, given daily during a test period the results of the *in vitro* incubation of 200 gm. of beef muscle with from 150 to 300 cc. of human gastric juice at pH 2.5 to 3.5, 9 of the cases showed an effect qualitatively similar to the effect of the ingestion of liver or effective liver extract. Fig. 1 shows clearly that in 8 of the 9 cases the effect of this therapy in producing reticulocytes was equivalent to that of 135 to 225 gm. of prepared liver daily.[5] In 7 of the 9 cases this therapy was continued sufficiently long to produce increases of over 1,000,000 red blood cells per c.mm. by the end of twenty days. In the 2 cases complicated by a cystitis and consequently showing a poor response to maximum dosage with liver extract of known potency, there were respectively no response and a poor response.

Discussion. From the observations made on this group of patients it would appear that an interaction between beef muscle and fresh human gastric juice produces from these two completely or relatively inactive constituents some substance capable of causing the appearance of a characteristic remission in certain cases of pernicious anemia. That in order to produce this effect an interaction of the gastric juice and the beef muscle is essential is evidenced by the fact that the gastric juice alone was shown to have no effect, and that from previous observations[1] the inactivity of beef muscle alone has been demonstrated. In the present series of experiments, it was shown that if the two constituents of the reaction are treated individually as far as possible, just as is to be done during the subsequent period of their effective interaction *in vitro*, but are kept separate and separately administered to the patient, there is either no effect or no effect of a magnitude comparable to that resulting from their subsequent free interaction.

Since the effect of this incubation of the gastric juice with beef muscle *in vitro* was quantitatively similar in 8 of the patients so treated to that observed in 8 of the previous series of 10 patients to whom were given the contents of the normal human stomach recovered during the digestion of beef muscle (Fig. 1), it seems reasonable to assume that the similar results of the two types of experiments represent an identical process carried out entirely as an *in vitro* reaction in the present instance. In the previous series of experiments,[1] it was shown that beef muscle itself was inert in terms of these reactions. In the present series, the ineffectiveness of gastric juice has been established, and thus the possibility of its direct action as a water-soluble extract of a highly cellular organ has

been excluded. Only the alternative of an action of the gastric juice on the beef muscle remains. It appears proper, therefore, to conclude that in the normal human stomach during the act of digestion of beef muscle there is formed by some action of the gastric juice on the meat a substance capable of markedly relieving the anemia and improving the clinical condition of those suffering from pernicious anemia. It is believed that this effect demonstrates for the first time a relationship of the human stomach to the function of the bone marrow. The general improvement in the sense

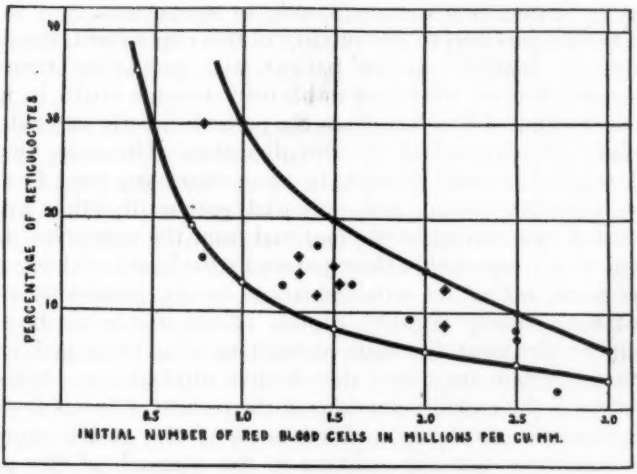

FIG. 1.—The respective maximum percentages of reticulocytes produced in 8 cases of pernicious anemia by the daily administration of the contents of the normal human stomach recovered one hour after the ingestion of 300 gm. of beef muscle are plotted (circles) against the initial red blood-cell counts of these patients. For 8 other cases similar data are recorded (diamonds) as a result of the daily administration of the products of the incubation of 200 gm. of beef muscle with from 150 to 300 cc. of fasting normal human gastric juice secreted after the subcutaneous injection of histamin. The upper curve represents the usual maximum reticulocyte percentages produced by the feeding of about 225 gm. of prepared liver daily to cases of pernicious anemia. The lower curve shows the usual effect of about 135 gm. of liver fed daily to cases of pernicious anemia. It will be seen that the respective maximum on 16 cases treated either by *in vivo* or *in vitro* digestion of the beef muscle with human gastric juice fall in the main between these 2 curves.

of well being, appetite, body weight, and activity of these patients, suggests an important effect on the general metabolism. The striking influence of a remission in one of these patients on the blood cholesterol has been reported elsewhere.[6]

In contrast to this is the demonstration from observations on 3 of the patients of the first group[1] that no comparable reaction can be obtained by administering to patients with pernicious anemia, under conditions most favorable to digestion and absorption, finely ground beef muscle in large amounts. Since it has been shown in

the present series of experiments that the positive effect depends upon the action of the normal gastric juice upon the meat, it seems possible to explain the ineffectiveness of the meat administered as such to pernicious anemia patients by the well-recognized deficiency of their gastric juice. As it is exceedingly difficult to secure any considerable quantity of the gastric secretions of patients with pernicious anemia, no attempt was made to carry out an *in vitro* experiment comparable to that performed in the present group of cases with normal human gastric juice. It was considered that the more significant experiment of the two had already been carried out *in vivo* by feeding beef muscle directly to the patient.

A possible objection to the validity of this experiment, considered to show the inability of the patient with pernicious anemia to produce an effective substance in his own stomach might be raised, since the feeding of beef muscle to the patient directly precluded the possibility of a period of *in vitro* digestion. However, the beef muscle was fed in small amounts in a fine suspension most favorable to any digestive action, and potential gastric digestion was not interrupted by removal of the material from the stomach. In one experiment not reported in these papers hydrochloric acid was added to the meat before its administration to the pernicious anemia patient with equally negative results. Even if it could be shown that under the most favorable conditions of a prolonged *in vitro* digestion a certain amount of the effective substance was formed by the action of the gastric secretions of the patient, the significance of the demonstration of the ineffectiveness of the gastric secretions under conditions actually existing in the stomach of the patient during the development of the disease would not be set aside. Conceivably, also, without the *in vivo* experiment, in the event of a negative result, an objection to the *in vitro* process on the grounds of some unknown artificiality could be raised. It seems proper, therefore, to consider this experiment valid in support of the contention that there is a striking difference in the ability of the stomach of the normal man and that of the pernicious anemia patient to produce the effective substance.

Since much attention has been directed to the possible rôle of the absence of hydrochloric acid in the production of this disease, it seems worth while at this stage of the observations to point out that the effects seen cannot be due to this substance alone or to its individual action on the beef muscle. In the experiments on those patients to whom were given separately in the control periods gastric juice and beef muscle after incubation with hydrochloric acid, there was either no evidence of a reaction in the control period (Case 17), or evidence of a significantly greater reaction when the beef muscle was incubated with both hydrochloric acid and gastric juice (Case 16) in the subsequent test period. (See table.) If the

hydrochloric acid itself had been the sole basis of the effect seen in the test period, a similar effect should have appeared in the control period. On the other hand, there is evidence that a large amount of hydrochloric acid may actually prevent in some way the action of the effective substance. An inspection of the data in the control period of Case 2 of the first series of experiments[1] shows that until the hydrochloric acid added during the incubation of the gastric contents *in vitro* was partly neutralized (pH 2.5 to pH 5) before administration of the material to the patient, no effect occurred. On changing the reaction of the material to pH 5, by the addition of sodium hydroxide, a remission was at once forthcoming in the test period. In the next paper of this series, further evidence of the negative effect of hydrochloric acid itself upon beef muscle will be presented.

The evidence from these experiments is thus quite in accord with the conception of pernicious anemia as a deficiency disease resulting from an inadequate digestion of protein imposed by the obvious lack of gastric juice of the pernicious anemia patient. It is clear that the normal individual can produce during the gastric digestion of beef muscle some substance which by transference to the stomach of the pernicious anemia patient will alleviate the symptoms of the disease. If it may be assumed that the quantitative nature of this effect and that of liver feeding is evidence of a deficiency disease, it is certainly reasonable to assume, as in other deficiency diseases, that the administration of the substance that will relieve the disease once developed will be able to prevent originally the development of the disease. By this reasoning, Addisonian pernicious anemia stands revealed as, in all probability, a disease dependent for its production in the last analysis upon the plainly defective gastric juice of the patient, which is incapable of elaborating the preventive substance shown in these experiments to be formed by the action of normal gastric juice on beef muscle. Since this substance is produced under conditions obviously permitting the peptic digestion of protein, it is possible that lack of this action is the intimate nature of the defect. Experiments designed to throw further light on this problem will be reported in the next paper of the series.

Summary and Conclusions. 1. The validity of the hypothesis that the development of the disease pernicious anemia is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the presence of a diet adequate for the normal man, has been further examined.

2. The results of the following experiments are considered to add greatly to the probability of the hypothesis.

(*a*) To 3 cases of pernicious anemia were given daily 150 to 300 cc. of incubated gastric juice secreted by fasting normal men after histamin injection. In 2 of these cases the gastric juice was incubated

for two hours with an indifferent protein, and in none of these patients was there evidence of effect on blood formation within fourteen days.

(*b*) To 4 cases of pernicious anemia were given daily for ten days in the afternoon 300 cc. of incubated fasting gastric juice secreted under histamin stimulation, and in the morning 200 gm. of beef muscle, incubated in 2 of the cases with hydrochloric acid, and in the other 3 with water. In 2 of these cases no effect on blood formation was observed within fourteen days. In 1 case a slight effect occurred and in another a distinct effect on blood formation was observed. However, in all of these cases a much greater effect was seen when similar quantities of gastric juice and beef muscle were incubated together. In a fifth case, complicated by cystitis, no effect was seen with either set of conditions.

(*c*) To the 8 cases just referred to and to 2 others were given 150 to 300 cc. of fasting human gastric juice secreted under histamin stimulation, incubated in the presence of hydrochloric acid at PH 2.5 to 3.5 for two hours with 200 gm. of beef muscle. In all but 2 of these 10 cases an effect upon blood formation was observed comparable to that seen with the similarly treated normal gastric contents in the first series of patients. Before the tenth day, there appeared an increase of the immature red blood cells followed by a progressive improvement of the anemia comparable to that ordinarily seen with the daily ingestion by similar patients of from 135 to 225 gm. of prepared liver. (Fig. 1.)

3. It is concluded, therefore, that by some interaction of normal human gastric juice and beef muscle, both of which have been shown to be individually ineffective, a substance can be developed which is capable of promptly and markedly relieving the anemia of certain patients with Addisonian pernicious anemia.

4. Since it has been shown in the experiments reported in the first paper of this series, that the presence of beef muscle in the stomach of the patient with pernicious anemia is incapable of developing such an effective substance, the conception of the absence of this effect as being due to the defective quality of the gastric secretion of the patient is strongly suggested.

5. It is believed that the correlation between the production of an effective substance and the presence of a normal proteolytically active gastric juice in contrast to the demonstrable lack of both in the patient with pernicious anemia, adds strength to the validity of the original hypothesis of the particular nature of the disease.

6. It is believed that for the first time a relationship between the stomach and the function of the bone marrow of the human being has been demonstrated; and the general belief that the integrity of the stomach is unnecessary to proper body metabolism brought into question.

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WHAT IS THE RISK OF INSURING APPLICANTS WITH PEPTIC ULCER?*

By Walter C. Alvarez, M.D.,

Associate in Section in Division of Medicine, The Mayo Clinic, Rochester, Minn., and Associate Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.

In order really to answer the question expressed in the title I should first of all be a trained actuary and then I should have at my disposal records extending over fifty years and showing when and exactly why 1000 men and women with definite duodenal or gastric ulceration died. Unfortunately, I am not an actuary and the follow-up data at my disposal are anything but complete. Under the circumstances, all I can hope to do is to give you such impressions as a clinician can obtain as he studies his patients, and such information as he can derive from the answers to questionnaires.

Because it is so hard to keep in touch with many of the persons who have passed through our hands we have to learn much of what we know from the stories of those who, when they come to us, have already suffered for from five to forty years; in other words, we try to get some idea of the future by looking into the past. One of our greatest handicaps in this study is that modern gastrointestinal diagnosis and surgery date back only fifteen or twenty years, and hence no matter how carefully we search we cannot expect to find many patients with ulcer definitely localized in duodenum or stomach before 1910 or 1915. Remember that it was in 1908 that

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W. J. Mayo pointed out the importance of the pyloric ring and showed that more ulcers are to be found caudad to it than orad. Remember also that the first roentgenoscope to be made in quantity in America was shown at the Panama Pacific Exposition in 1915. My first one, secured in 1912, had to be imported from Vienna.

In order to begin, let us imagine that 100,000 men and women of all ages applying for insurance, have experienced some indigestion. Possibly half of them, or 50,000 will have so little distress or so little spare cash that they will never consult a physician. Some will prescribe for themselves, some will consult a druggist, a chiropractor, or an osteopath, and some will trust to Christian Science and other forms of faith healing. Many in this group will doubtless suffer with peptic ulcer and never know it. My reason for making this statement is that the pathologist who is particularly interested and who will look carefully, will often find the puckering scars of duodenal ulcer, and when he questions the relatives he will sometimes be unable to obtain evidence that the deceased ever complained of indigestion.

Robertson and Hargis found such scars in 6.1 per cent of 2000 bodies examined at The Mayo Clinic. This figure is almost twice that representing the incidence of gastric and duodenal ulcer as diagnosed by our roentgenologists (3.3 per cent of 71,675 patients registered in 1926). From England, Souttar reports that 4.3 per cent of 30,000 patients admitted to the surgical wards of the London Hospital were suffering with ulcer.

Robertson and Hargis found active ulcers in 12.8 per cent of the bodies, but this figure does not throw light on the problem before us, first, because the material studied does not represent a fair sampling from the community, and second, because so many of the lesions were probably recent and due to the serious illness that produced the death of the patient. Ulcers or scars were found in 378 of the bodies examined. If we exclude the 163 cases in which an operation for ulcer had been performed, we will have 215 or 10.7 per cent (of the 2000) in which an ulcer or scar may have been found accidentally. As 21 per cent of the gastric and 40 per cent of the duodenal ulcers were healed, active ulcers must have been found unexpectedly in, at the most, 7.4 per cent (of the 2000) and scars in 3.4 per cent. The figure 3.4 is the one which I think should interest us particularly in this discussion because it gives some idea of the percentage of men and women in America with healed ulcers.

In Robertson's experience ulcers are found commonly (in decreasing order of frequency) in association with diseases of the thyroid, the kidney, the prostate (commonly associated with destruction of the kidney), the gall bladder, the brain and cord, and the appendix.

Incidentally, this brings up a point which should be of interest to the insurance examiner when he is appraising the risk of an applicant who has or has had trouble with peptic ulcer. Such persons, and

especially the women, are likely to have other forms of disease in the abdomen for which they may eventually be operated on, and every such operation naturally carries with it a risk. Some idea of the frequency of these complications of ulcer may be seen from Table I. Such tables would be much more enlightening if the surgeon would always examine the gall bladder and appendix and record his impressions in regard to them, but this he is often loath to do, especially when he is hurrying to complete a difficult resection of the stomach.

TABLE I.

	Duodenal ulcer, surgically demonstrated.						Gastric ulcer, surgically demonstrated.					
	Men.			Women.			Men.			Women.		
	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.	Cases.	Totals.	Per cent.
Gall bladder disease:												
"Normal"	40			58			35			29		
"No stones"	17			3			8			24		
Not described	11			24			39			22		
		68	68		85	61		82	77.3		75	71.5
Drained previously				4								
Removed previously	2			5			2			5		
Removed here: Stones	2			15			1			3		
No stones				10								
"Cholecystitis"	6			3			3			2		
Stone present, not removed				1			2			4		
Wall thickened markedly	1						1					
		11	11		38	27		9	8.5		14	13.3
Wall thickened	2			4			4			4		
Wall thickened slightly	3			6			2			4		
Perihepatitis				1						1		
Adhesions about gall bladder	8			6			3			3		
Contracted gall bladder	1											
Large glands on common duct	1											
		15	15		17	12		9	8.5		12	11.4
"Not examined"	6									4		
		6	6				6	6	5.7		4	3.8
Total cases		100			140			106			105	
Appendectomy:												
Done previously		13			39			13			24	
Done here with operation on ulcer		71			44			50			34	
Pelvic disease:												
Not operated on					11						9	
Operated on					19						22	

All we can say from the records available is that definite gall bladder disease was present in at least 8.5 or 11 per cent (8.5 with

duodenal ulcer and 11 with gastric ulcer, Table I) of the men with ulcer and in from 13.3 to 27 per cent of the women (Table I). As one would expect from the propinquity of gall bladder and duodenum, cholecystitis was found more frequently with duodenal than with gastric ulcer.

It is impossible to say how much real disease of the appendix there was in these patients but the records show that by the time they were operated on for the ulcer, 13 per cent of the men and from 24 to 39 per cent of the women (24 in the group with gastric ulcer and 39 in the group with duodenal ulcer) had submitted to appendectomy. That these figures are somewhat higher than normal is shown by the fact that Blackford found that 13 per cent of 1000 patients who consulted him in regard to indigestion had parted with the appendix. In women many appendices are removed at the time of operations on the pelvic organs, and in the group of 244 women with ulcer which I studied, from 19 to 22 per cent had submitted to operation for pelvic disease.

But to return to the hypothetical group of 50,000 men and women who are going to physicians because of indigestion: can we make any guess as to the number who are suffering with peptic ulcer? I think we can. At The Mayo Clinic in 1926, 13.7 per cent of the 15,000 patients examined roentgenologically on account of indigestion were found to have duodenal deformities interpreted as due to ulcer, 1.5 per cent had gastric ulcer and 0.3 per cent had ulcers in both stomach and duodenum. If these percentages were the same in the hypothetical group, there should be 6850 with duodenal ulcer, 750 with gastric ulcer and perhaps 150 with gastric and duodenal ulcer. Actually these figures are probably too high because so many persons with particularly resistant ulcers come to us from far distant places and thus interfere with the evenness of the sampling from the Middle West where we get most of our patients. This error may be compensated, however, by the fact that we doubtless fail to diagnose many ulcers.

Statistics which I gathered several years ago show that the average practitioner, unaided by expert roentgenologists, will make the diagnosis in only one-third of these cases. The insurance examiner is likely, therefore, to hear of only 2580 cases of ulcer in the group of 100,000 instead of the 16,000 or more in which he ought to be informed of the presence of the disease.

What now is going to happen to the 2580? Before I attempt to answer this question I must first emphasize the importance of distinguishing between those persons with duodenal ulcer and those with gastric ulcer. As will be shown later the mortality rates are different and the problems of treatment are different.

Treatment of Duodenal Ulcer. Turning first to a consideration of duodenal ulcer I will remind you that there are four main types of treatment commonly adopted. The first and probably the most

common, even among physicians suffering with ulcer, is treatment by neglect. In the early stages of the disease the results of such treatment are often good and so far as is known, perhaps just as good as those obtained by careful treatment. Some of my confrères will doubtless be shocked at this statement but I have some statistical data which indicate that it is true. It must be noted, however, that I said "in the early stages of the disease." Unfortunately, in perhaps half of the cases (I have no way of estimating this figure more exactly) the disease eventually becomes so severe and so resistant to ordinary home treatment that something more must be done.

The second form of treatment is an ambulant one in which the patient stays at work and takes food and perhaps alkalies every two hours. It works well in many cases and commonly gives prompt relief. The problem in ulcer, especially in the early years of the disease, is not so much to give relief: this is often easy; the difficulty is to prevent recurrences. The third form of treatment requires hospitalization and careful dieting, and the fourth requires the help of the surgeon.

Medical Treatment. Now what chance is there for permanent cure under the various forms of medical treatment? I cannot say because most of the follow-up studies so far made cover periods of only a few years. The recent report of Blackford and Bowers indicates that the intervals of relief after careful hospital treatment are no longer than those secured after ambulant treatment, and this agrees with my own impressions. The statement that in their experience the end results of medical treatment are as good as those after surgical treatment is somewhat surprising but to a certain extent it agrees with the observations of others. It does not mean, of course, that surgical treatment with its greater risk and suffering and expense should be given up. We cannot give it up because in a large percentage of cases the time comes when medical treatment no longer brings relief and the patient finds himself incapacitated and exhausted by suffering. The ulcer has perhaps perforated into surrounding tissues, it is bleeding, or it has mechanically closed the outlet of the stomach. Under such circumstances surgical help must be invoked. That the surgeon fully recognized the limitations of his work and the possibilities of curé under medical care is shown by the fact that often he will refuse to operate until several attempts at medical treatment have been made or until the patient is definitely handicapped by the disease.

I shall not attempt here to review much of the literature on the remote results obtained with the medical treatment of peptic ulcer, because the subject has already been so well discussed in Chapter XLIII of Crohn's book on "Affections of the Stomach." He concludes that if the patient is young and in the first stages of the disease good immediate results can be obtained in three-fourths of

the cases. The difficulty is that these persons do not stay well and actually, the longer one keeps in touch with a group of them the more discouraged one gets.

In Einhorn and Crohn's series of 100 cases carefully treated in the medical wards of Mt. Sinai Hospital and followed from one to four years, the immediate results were excellent, and 86 were apparently cured. Most of them went six months without symptoms, but by the end of the first year 31 per cent of the 86 were back again with the same old trouble. With each succeeding year more cases had to be transferred from the list of the cured to those of the relapsed until by the end of four years, the two groups were about equal. Furthermore, by this time nineteen out of the original 100 patients had turned to the surgeon for relief. Of the group of 22 patients who were observed for the full four years, 7, or 32 per cent, were operated on.

Of the whole group 3 died, 1 of cancer of the lung, another of pulmonary tuberculosis, doubtless aggravated by the severe ulceration of the stomach, and 1 from perforation of the ulcer. Einhorn and Crohn could then, at the end of four years, claim only 27.3 per cent of apparent cures after careful hospital treatment. If they had included the cases in which improvement was noted, the figures would have been 90 per cent for the first few months and 50 per cent for the four years.

Results similar to these have been reported by Barford in England and by Smith in Scotland. Smith, who groups gastric and duodenal ulcers together because he says they are so hard to differentiate, reports that 24 per cent of the men and 8 per cent of the women treated medically had later to be operated on. Interesting from the insurance point of view was the fact that 21 per cent of the men and 19 per cent of the women were eventually so incapacitated by the disease that they were unable to work. In addition there were 16 per cent of the men and 12 per cent of the women who had to turn to lighter jobs.

Forsyth, chief medical officer of a British Assurance Society which makes a specialty of life and health insurance for physicians, has published some figures which, while few in number, are of unusual interest and value because the subjects were almost all physicians, because half were operated on and half not, and because with a sickness-indemnity provision in the policies the company was able to keep a record of recurrences and of the amount of disability suffered. Unfortunately, the insured were observed for periods of only from one to twelve years.

Of the 59 in the series, 22 or 37 per cent relapsed from one to seven times. Fifty-six per cent were operated on, apparently most of them during the period of observation. The number reporting recurrences was practically the same in the two groups but the number of relapses for each person was a little larger in the group treated medically. One such relapse took place as late as ten years

after the apparent cure of the disease. Four of the 33 treated surgically had to have secondary operations: one of them after sixteen years. Two of those operated on died in the hospital and one more died later. Forsyth concludes from this that persons with duodenal ulcer may perhaps be given life insurance but they certainly should not be given sickness insurance.

Bleeding. Aside from the risks of operation the two accidents that may cause death in these patients are hemorrhage and perforation. Most observers agree that from 15 to 30 per cent of persons with ulcer will at some period of the disease bleed severely; but fortunately in only about 1 per cent of all the cases of ulcer does such bleeding cause death. According to Barford, in England, bleeding is six times as common with duodenal as with gastric ulcer, but according to Moynihan it is three times as frequent with the gastric lesions. According to Balfour (1927), gross hemorrhage occurred in 18 per cent of 1072 cases of duodenal ulcer operated on. This bleeding was six times as frequent in men as in women. Gross hemorrhage was seen in about 20 per cent of the cases of gastric ulcer.

Perforation. Many ulcers perforate but only a small percentage break through the wall of the stomach or bowel so rapidly that gastric contents can soil the peritoneal cavity. When the symptoms are promptly recognized and an operation is immediately performed most of these patients recover. In Scotland, Smith found perforation was responsible for 2.8 per cent of deaths in all types of ulcer. According to Moynihan perforation is half again as frequent with gastric as with duodenal ulcer. Gibson studied 60 cases of acute perforation. Twenty-eight were in cases of gastric ulcer and 32 were in cases of duodenal ulcer. If in his material there was the usual ratio of 8 duodenal ulcers to 1 gastric it must be that the gastric lesions are seven times more subject to perforation than the duodenal. The mortality in the gastric cases was 21 per cent and in the duodenal 12 per cent.

Surgical Treatment. As I have already intimated, a considerable number of patients with duodenal ulcer should be operated on as soon as they are seen by the consulting gastroenterologist. Others should accept surgical help only after the inefficacy of medical treatment has been demonstrated. What then will be their chances of recovery?

With a really expert surgeon the immediate mortality should be small, and if the usual operation of gastroenterostomy is performed all but 2 or 3 out of 100 patients should walk out of the hospital. Unfortunately such a low mortality is secured only with surgery at its best and the actuary dealing with this problem will have to allow for the possibility of a much larger percentage of loss after operations.

In the five years following operation the chances of cure or

considerable improvement appear to be between 70 and 90 per cent. Balfour reported, in 1925, that 88 per cent of 1000 patients with duodenal ulcer, operated on ten or more years before, were relieved. In 1927, he reviewed the results in a group of 100 physicians operated on. This study is particularly enlightening because the subjects were all fairly intelligent and all competent to appraise the degree of relief obtained. Their average age was forty-seven years and the average duration of symptoms was thirteen years, so it will be seen that most of them belonged in that group of patients in whom medical treatment is usually of little avail. It was all the more cheering, therefore, to find that after intervals averaging eight and a half years, 84 could report a satisfactory result. Six more, while not entirely relieved, believed that the operation had helped and that it had been worth while. Five had been operated on again, 2 for recurring hemorrhage, 1 for reactivation of the ulcer and 2 for gastrojejunal ulcer. Some of those finally obtained relief, and only 5 of the original group remained unimproved. Similar results have been reported from England by Moynihan, Walton and Broster.

Fremont-Smith and McIver at the Massachusetts General Hospital have recently made a valuable study of the results obtained after operation on 393 patients with duodenal ulcer and 261 with gastric ulcer, observed for periods ranging up to ten years. I will discuss at this point only their results with duodenal ulcer. The immediate mortality was 7.6 per cent, and 4.6 per cent more are known to have died since leaving the hospital. Eighty per cent of the 261 patients watched for a year reported good results. Recurrences soon began to appear, however, and more and more cases had to be transferred from the list of the cured to the list of the relapsed.

Figure 1 shows that the percentage of patients with severe recurrences rose gradually from eight at the end of the first year to nineteen at the end of six years. After that it appeared to drop off a little. The figures suggest that if a patient operated on for duodenal ulcer can get past the sixth year without a recurrence his outlook will be good. If he has had recurrences by this time the chances are that these are going to incapacitate him more and more as years pass. There is some hope also that the patient with gastric ulcer will be fairly safe if he gets past the eighth year without recurrence. We know that reactivations take place after intervals of ten years but we cannot say yet how common they are.

We must conclude, then, that even the best of surgical treatment will not entirely erase that remarkable tendency to recurrence, perhaps hereditary,* which is seen in a number of patients with

* Smith found that in 8 per cent of the men and 12.7 per cent of the women with ulcer one or both parents and one or more brothers or sisters were similarly affected. Reich has described a family with peptic ulcer appearing in four generations. At The Mayo Clinic we have the impression that this tendency is more marked in the Jew than in other racial strains and at times it is seen strikingly in the nervous, high-tension, go-getter, sales-manager type of man.

ulcer. No matter what is done for them the disease flares up again and again, and some have to go from one operation to another. This is particularly true of that group of unfortunates who are subject to the formation of chronic gastrojejunal ulcers—perhaps 2 per cent of all who submit to gastroenterostomy.

In spite, however, of all these difficulties and dangers, the careful follow-up study by Balfour and Hunter of 1651 persons with duodenal ulcer, operated on and watched for periods averaging 3.4 years showed that the mortality was a little lower than that of a control group of men and women with a similar age distribution, observed for the same length of time.

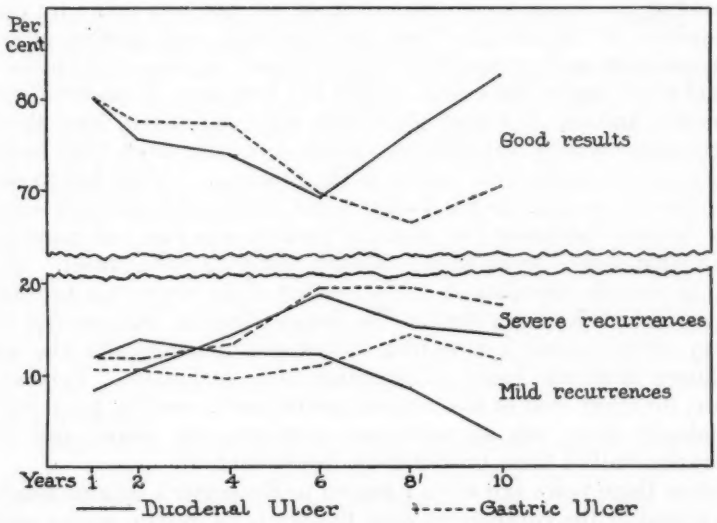

FIG. 1.—The late results of the surgical treatment of ulcer; a graphic representation of data published by Fremont-Smith and McIver.

Gastric Ulcer. The clinical pictures of gastric and duodenal ulcer are so similar that when a patient comes with the story of "hunger pain" returning in attacks once or twice a year, the expert does not attempt to say whether the lesion is above or below the pylorus. As a betting proposition he knows that the odds are about 8 to 1 in favor of its being below, but he makes no decision until he hears from the roentgenologist.

But if the diseases are so indistinguishable why worry about a difference of only a few centimeters in the location of the lesion? Because, if the ulcer is in the duodenum the fear of cancer can practically be dismissed, while if it is in the stomach the possibility of malignant degeneration must ever be kept in mind. I make this statement unequivocally and I am going to emphasize it in spite

of the fact that some gastroenterologists will still disagree with me. In 1923, when Jones sent a questionnaire to the members of the American Gastroenterological Association asking them how often they had seen a cancer develop in a gastric ulcer, some said they had never seen it, others thought it occurred in from 1 to 5 per cent and most of them thought the danger was so small as to be almost negligible.

Now, whenever two groups of reputable men of science disagree it generally appears later that both were partly right and both partly wrong, and usually because neither paid careful attention to see exactly what the other was talking about. One has only to look over the statistical reports on which many of the statements in the literature are based to see that little or no care was taken by the compilers to discriminate between duodenal and gastric ulcer. Obviously in such groups, made up principally of patients with duodenal ulcer, one would expect to find but few cases of cancer of the stomach, and the fact that physicians still continue to base their arguments on such statistics only shows how completely they have failed to comprehend the nature of the problem. Others fail to see or refuse to see that the big danger is not that an old ulcer will some day become cancerous but that the patient who has just come in with what looks like an ulcer is already suffering with cancer. We can as yet only speculate as to the number of old ulcers that become cancerous but we know that at The Mayo Clinic in 1926 one out of every seven gastric lesions that looked roentgenologically like an ordinary ulcer was found at operation to be malignant. Furthermore, for every four or five typical gastric ulcers seen by the roentgenologist there was an additional indeterminate lesion, and at operation half of these proved to be carcinomatous.

Some three years ago when I moved to Rochester I became much interested in the controversy over the origin of gastric cancer and more and more desirous of examining the data and of forming an opinion for myself. At first sight it might seem that a man who for eighteen years had been seeing a large number of patients with indigestion should have had an opinion, but after a little study I found why I had none.

The difficulty is that gastric ulcer is a comparatively rare disease. In 1926, at the Clinic, with a registration of 71,675, the roentgenologists examined 15,000 who complained of indigestion and diagnosed gastric ulcer in 225 and multiple gastric and duodenal ulcer in 47. One hundred and ten of these (1 in 650 registrations) were operated on and the ulcers removed and made available for microscopic study. Only 11 of these lesions were more than 2 cm. in diameter and, as will be brought out later, these were the ones which were most likely to be cancerous. During the same period the roentgenologists diagnosed cancer of the stomach in 375 patients and found indeterminate lesions in 47 more. A little more than half of these

patients were operated on and 24 of the lesions removed were found to be less than 3 cm. in diameter.

There were, therefore, during the year, 35 cases in which the pathologist had to be particularly careful in distinguishing between a benign and a carcinomatous ulcer. This represents an incidence of one in 2050 registrations. If a similar ratio holds in private practice then a physician who studies let us say 700 new patients a year and who has half of those presenting gastric lesions operated on by surgeons competent to do a resection will see one of these borderline lesions every three years. Under such circumstances he can hardly recognize the problem, much less form an opinion about it. We, on the other hand, who see one of these cases every ten days become greatly interested in them and become convinced of the great need for handling them properly.

But some may say, "Why bother about these cases if they are so rare?" The answer is that all cancers of the stomach must some time have a beginning and when they begin they almost certainly must be small. But where will we find some to study? Obviously, as they rarely cause death until they have extended widely we must find them accidentally at necropsies and at operations on the stomach. And what do they look like then? Very rarely a little adenomatous plaque is found; less rarely a polyp with malignant changes at some point, and commonly—and this is the important point—cancer is found in the walls of what looks like a large benign ulcer. It would seem obvious, then, that the only way in which we can every hope to get at early cancer of the stomach is to excise gastric ulcers.

These views are not based on observations made only at The Mayo Clinic. Wilensky and Thalhimer who made a careful study of 48 ulcerlike lesions classified 7 as carcinomas. One more was an ulcer with carcinomatous changes here and there along the edges and one was an apparently benign ulcer with the adjacent lymph glands full of cancer. Such cases have been seen several times by MacCarty.

In 1000 stomachs studied at necropsy, Cleland found cancer in 36. In 5, the lesion was small and was discovered only accidentally. One was a small papillomatous mass with malignant degeneration, one was a polyp with a malignant ulcer at the base and 3 were ulcers with carcinomatous changes in the wall. Although this change could be detected only microscopically, in 2 it was associated with widespread metastasis. Incidentally, the fact that this early dissemination of metastases is noted with a third of the small carcinomatous ulcers removed at The Mayo Clinic should somewhat silence those who still hold that our pathologists are mistaken as to the nature of the cell changes in the lesion itself. Apparently, then, in a series of 36 cancers of the stomach found at necropsy, 1 in 7 was unexpected and 1 in 12 was in the wall of an ulcer.

Stewart at Leeds studied 134 chronic gastric ulcers, 14 cancers apparently arising in chronic ulcers, and 68 cancers in which he could find no sign of ulcer. All were removed at operations. He concluded that 9.5 per cent of the chronic ulcers had become cancerous or 17 per cent of the cancers had originated in ulcers. Moynihan, with his great experience, believes that one cannot neglect the danger of cancerous degeneration in gastric ulcers. He expresses himself as feeling "acutely anxious as to the destiny of any patient suffering from gastric ulcer."

That the problem is a big one and that conditions cry out for improvement was shown in a recent paper by McVicar and Daly. They found that at The Mayo Clinic, in the five years from 1920 to 1924 inclusive, 2078 patients were seen with carcinoma of the stomach. Of these, one-half had to be sent home immediately as hopeless; the other half were operated on, but again, in only half could any attempt be made to remove the tumor. Three-fourths, then, of the cancers of the stomach which we now see are so large that nothing can be done about them.

The next question is: Who is to blame? In many cases no one is because the patient, with hardly a symptom, does not suspect his danger until the disease is far advanced; in others, members of our profession are to blame because for weeks and months they tried out one remedy after another for what they thought was transient indigestion or benign ulcer.

As I have already pointed out, many gastroenterologists today still have the idea that when we at The Mayo Clinic ask a patient with gastric ulcer to be operated on it is because we are afraid the lesion will later become cancerous. Although we do see many cases in which the history strongly suggests that this is a contingency to be feared, we are really more concerned with the possibility that the lesion before us, which looks like an ulcer, may already be malignant.

Often, of course, when we are dealing with a fairly young patient with a history running back several years, with normal amounts of hydrochloric acid, and a very small ulcer, we know that the odds are strongly in favor of its being benign. But this does not entirely satisfy us because with the large numbers of patients constantly going through our hands not a month passes that some one does not appear to startle us and sober us by breaking all the rules of statistical expectation.

Some physicians depend a good deal on the age of the patient but Fig. 2 shows that when it comes to making a diagnosis, the differences between the age distributions of patients with gastric ulcer and gastric cancer are too small to be of service. No one of us would care to risk his life on a "two to one shot."

With the training that we physicians had at college, it is hard for us to think of a ruddy, robust and perhaps slightly overweight man of forty years as having cancer of the stomach, and yet obviously

cancer must at some time in its course be so small as not to produce any symptoms, and certainly not such severe ones as emaciation and anemia. For years my associates at the Clinic have been trying to get physicians to see that our textbook pictures of carcinoma of the stomach, the pictures which we present to our medical students, are highly inadequate and misleading. We perhaps ought even to hide them because they are the pictures of cancer in its final and usually hopeless stage.

What we should be hammering home is the conception that early cancer must be looked for in normal, healthy looking men and women with only a slight deformity in the outline of the barium-filled stomach. Until this idea can be incorporated into that mass of medical impressions upon which all of us, physicians and laymen

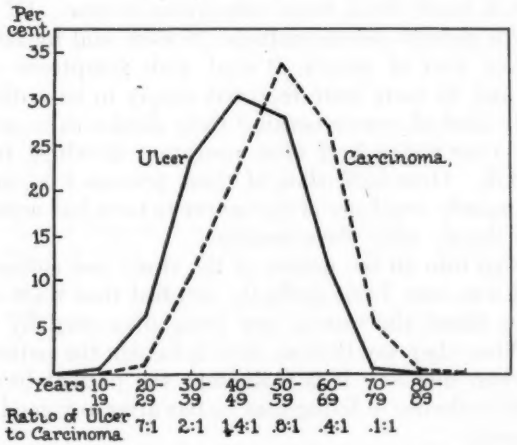

FIG. 2.—Percentage distributions showing the ages of 500 patients with gastric ulcer and 2086 patients with cancer of the stomach. The figures on the lowest line indicate the relative numbers of ulcer and cancer bearing patients at different ages.

alike, base our actions there is little use in talking about the early diagnosis of cancer of the stomach.

The objection may, of course, be raised and it is being raised, that the early carcinomatous changes seen by the pathologists at The Mayo Clinic may be but figments of their imagination. In order to satisfy my mind on this point I some time ago took advantage of Dr. MacCarty's kind offer to go over with him the hundreds of records collected in his laboratory in the last eight years. To simplify the problem I put aside the records of small ulcers and large cancers about which there can be little or no question and concentrated my attention on ulcers larger than 3 cm. in diameter and carcinomas smaller than 4 cm. in diameter. I did this because it seemed to me so obvious that if mistakes had been made, almost

all of them would be found in this borderline group of the largest ulcers and the smallest cancers.

With the help of Dr. Balfour's follow-up service I next looked up the subsequent history of the 126 patients from whom these possibly questionable lesions had been removed. Of the 15 with ulcers smaller than a half dollar (799 sq. mm.) all but one (who was a syphilitic) were in fair or good health when last heard from. Of the 8 with supposedly benign ulcers larger than a half dollar, 5 had died with what was either probably or certainly cancer of the stomach. Evidently then ulcers larger than a half dollar are almost always cancerous and our pathologists are not yet quite radical enough in recognizing early malignant changes.

The records of only 68 of the patients with "cancer" could be used in this study, the others having been operated on too recently for me to tell much from their subsequent course. Of the 68, 3 returned with general carcinomatosis; 16 were said by home physicians to have died of cancer, 2 died with symptoms suggesting recurrence, and 15 more were reported simply to have died. They too probably died of cancer because their demise came within that period of a year and a half after operation in which recurrences commonly kill. Over half, then of these persons who would seem from the unusually small size of the cancer to have had a good chance for life died shortly after the operation.

I will not go into all the details of the study but suffice it to say that when I was done I felt perfectly satisfied that there is nothing make-believe about the cancer now being diagnosed by our pathologists. When they say that an ulcer is benign the patient usually lives and when they say it is malignant the patient has only the usual fifty-fifty chance of living that he has after any good operation for early cancer.

As I have already said, we at The Mayo Clinic, even at the time of operation, know of no way of telling, except by examination of microscopic sections, whether an ulcer is or is not cancerous. Large lesions and especially lesions that produce filling defects are almost certainly malignant and with them a good roentgenologist seldom misses the correct diagnosis. But, as even Cole with his careful technique has admitted, when a lesion is first seen, "in approximately 10 per cent of cases it is difficult or impossible to state definitely from the radiologic evidence alone whether the case is one of simple ulcer or of cancer." This being true, where is one to get help in the diagnosis?

There is one point brought out in the history which is often very helpful in making a tentative diagnosis and that is the duration of the symptoms. Some time ago I examined 100 records of patients with benign gastric ulcer, proved by excision and microscopic section, and 100 records of patients with inoperable cancer of the stomach surgically explored. In Table II I have classified these histories

not only according to the duration of symptoms but also according to my opinion of the type of the history; that is, whether it suggested to me the presence of ulcer, of cancer, or of gall-bladder disease. Some of the stories were fairly typical for ulcer and others could only be called vague.

TABLE II.—THE LENGTH AND TYPE OF HISTORY OF INDIGESTION.

Mos.	Yrs.	100 patients with gastric ulcer operated on at The Mayo Clinic in 1925, 1926, and 1927.	Totals.		100 patients with inoperable carcinomas of the stomach explored at The Mayo Clinic in 1926.	Totals.	
1		g	1		cccv	4	
2		vv	2		cccccc	6	
3					ccccccc, obstr. at cardia	8	
4		uvv	3		ccccvu	6	
5		v	1		cccccvv	7	
6		c	1		ccccccccccv	11	
7					cvv	3	
8		u	1		ccv	3	
9					c	1	
10		u	1		cc	2	
11					c	1	
	1	ug	2	12	ccccccccccvvu, obstr.	15	67
	2	uuu, a-u, vcc	7	19	ccccvvvuuuu, p. anemia	12	79
	3	uuuffv	6		cvuu	4	
	4	uuf	3		u?	1	
	5	uuuvffff	8		u	1	85
	6–9	uuuuuuuuuuuuuvvvvvvvvffg	23		u, u?	2	
	10–14	uuuuuuvvvvff	12		uuu, u?, u?, u?, g	7	
	15–19	uuuuuuvvf	9		uv	2	
	20–24	uuuuuvf	7		ug	2	
	25–29	uuuuf	5		uu	2	
	30–34	uu, u-g, v	4				
	35–39	g	1				
	40	uvv	3				
			100			100	

ABBREVIATIONS: u represents ulcer; v, vague; f, fair ulcer; c, carcinoma; g, gall-bladder disease; a, appendicitis; obstr., obstruction.
Each letter or combination of letters represents a case.

It will be seen at a glance that a few of the patients with gastric ulcer came to the Clinic in the first or even the second year of the disease. Most of them had had symptoms for from five to thirty years. On the other hand, 79 of the 100 with cancer of the stomach had had symptoms for less than two years (Fig. 3).

No matter, then, what one thinks about the etiologic relationships of ulcer and cancer there is no getting away from the fact that it is very dangerous to treat medically any patient with a gastric lesion and a short history. Many physicians say, "Well and good, we admit that, but why not treat such a patient medically: if he improves and gains in weight we can stop worrying; if he does not respond properly we can call in a surgeon." This plan sounds reasonable but in practice it often fails, and not a month passes at

the Clinic that we do not see an example of the type of disaster that can result from placing reliance in it. The trouble is that although the cancerous lesion often fails to respond to ulcer management it does not always do so. Sometimes it responds beautifully; symptoms disappear, the patient gains in weight and everyone for a time is delighted. Later, when the collapse comes, metastatic nodules are everywhere and it is too late to do anything.

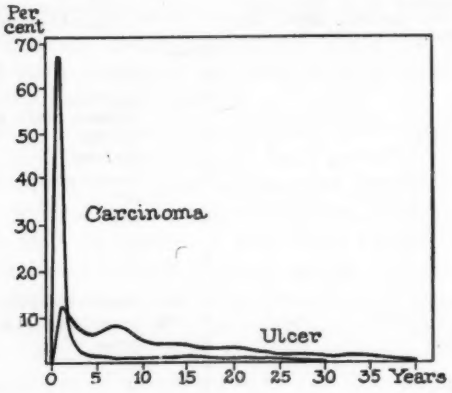

FIG. 3.—Percentage distributions showing the marked difference in the duration of symptoms in patients with ulcer and cancer of the stomach.

Doubtless there will always be cases of gastric ulcer which for one reason or another will have to be treated medically, and obviously, the most suitable subjects for such treatment will be the younger patients with a history of several attacks, a small ulcer, and perhaps normal gastric acids. But even in these cases, with the chances largely in favor of the lesion being benign, the conscientious physician will remain uneasy and will insist on watching the ulcer with the roentgenoscope until it either disappears or begins to grow larger.

I say this in spite of the fact, emphasized by many clinicians throughout the world, that there are many patients with gastric ulcer who can be treated medically for years without the appearance of cancer. A glance at Table II shows that this must be so, otherwise 19 out of 100 persons with gastric ulcer could not have lived as they did to tell a story of typical attacks of pain running back fifteen, twenty, thirty and even forty years. If we include 9 with fair or vague ulcer stories we have 28 out of 100 with symptoms for more than fifteen years.

Table II and Fig. 3 show also that patients with cancer of the stomach rarely admit having been ill for longer than two years, and that in only about 16 per cent does routine questioning bring out a story of symptoms suggesting ulcer running back more than

two years. Believing as I do that cancer commonly develops on the basis of ulcer, I am forced to the conclusion that ulcers which become cancerous are either of the symptomless variety or else the persons who bear them are peculiar; that is, they are so prone to malignant degeneration that the changes take place as soon as there is any break in the mucosa of the stomach.

A patient illustrating such a marked tendency to cancer formation was recently shown me by Dr. Bargen. The man came to the Clinic in 1922 with two distinct cancers in different parts of the colon. They were resected and five years later he returned with two more distinct cancers of the colon. One brother had died of cancer of the colon and another is now being treated at the clinic for the same disease. Probably Maude Slye is right and some of us are immune to cancer and others highly susceptible.

Somewhat against my theory is the fact that I have already found a few patients with old benign ulcers who now have cancer in the colon or prostate, but it must be remembered that in many persons, as in Miss Slye's mice, cancer susceptibility and immunity may be limited to certain organs or tissues. Another big objection to the ulcer-cancer theory is the fact noted in Table II that in only 2 out of the 67 cancer-bearing patients with symptoms for a year or less did the story sound to me like that of definite ulcer. Other clinicians might disagree with me but that was my impression obtained from the particular histories studied.

Of one thing I can be sure and that is that any form of indigestion or constipation, no matter how mild or vague, which comes out of a clear sky after the age of forty years, must be investigated immediately and thoroughly and with the help of a really expert roentgenologist. Certainly no applicant for insurance with such a story should be accepted until it is certain that the outlines of stomach and colon are normal, and even then he will bear watching.

One big reason why we should all be making an effort to estimate more exactly the danger of malignant degeneration in old chronic gastric ulcers is that the bearer of such a lesion cannot flee from this vaguely outlined menace without running into the very real danger of death from subtotal resection of the stomach. Under the circumstances, any patient who is at all inclined to reason statistically will want to know the probabilities; that is, he will want to balance the mortality rate for cancer against the mortality rate of the particular surgeon who is to operate on him. Seeing that physicians are daily being called on to help in making this decision, it is a shame that as yet, they have not at their command the information which they need.

The only "proof of the pudding" in insurance work comes through obtaining data on actual experience with a sufficient number of risks. Actually Balfour and Hunter showed in 1919 that after operations for gastric ulcer the mortality was higher than normal.

There were 521 patients observed for an average period of 3.6 years. The immediate surgical mortality was 4.5 per cent. During the period of observation 17 per cent died, while in the group of 1651 patients operated on for duodenal ulcer only 5 per cent died. Most of the excess mortality in the cases of gastric ulcer came in the first three years when carcinoma, missed at the operation, may have been taking its toll.

That actuaries still need more definite information is indicated by a paper published by Morgan in 1926. He wrote to eighteen representative companies to ask what their practice was in regard to applicants with a history of duodenal ulcer. Seven refused all with a history of gastric ulcer; seven accepted applicants with duodenal ulcer if free from symptoms for two years after surgical treatment or for five years after medical treatment, and two made the same ruling in regard to patients with gastric ulcer. Seven refused all applicants with duodenal ulcer not operated on and nine refused those with gastric ulcer not operated on.

Conclusions. Scars of peptic ulcer were found more or less unexpectedly during 3.4 per cent of 2000 necropsies performed at The Mayo Clinic, and open ulcers were found more or less unexpectedly in 7.4 per cent. Ulcers are diagnosed roentgenologically in about 3.3 per cent of the patients who register at the Clinic or in 15.5 per of those who complain of indigestion.

Women with ulcer often suffer also from gall bladder disease and they often submit to appendectomy and to operations on the pelvic organs.

Peptic ulcer is a serious disease based on some predisposition which in many persons causes the lesions to reappear again and again even after excision of part of the stomach.

In the early stages of the disease it is, in most instances, easy to relieve symptoms but in more than half of the cases they tend to recur.

The danger of death from bleeding or perforation is small.

Many of the patients with chronic ulcers must eventually be operated on and that carries a risk. For the first few years after operation the results are generally good but as years pass, an increasing number of the patients relapse; from 5 to 10 per cent have to be operated on again, and many become more or less incapacitated.

For this reason, persons with ulcer are not fit subjects for health insurance. Great care must be taken to distinguish between those with duodenal and gastric ulcer not only on account of the higher risk of operations for gastric ulcer but because there is a definite possibility either that the lesion is cancerous at the time of examination or that it will become cancerous later.

Persons past forty years with recently acquired indigestion of any kind are particularly undesirable as risks. It is impossible in many cases to distinguish, even at operation, between benign and malignant ulceration.

The only way in which to cure cancer of the stomach is to operate on healthy looking men and women with a slight but definite irregularity in the outline of the barium filled stomach.

Persons with duodenal ulcer might be accepted as substandard risks when, after either medical or surgical treatment, symptoms have been absent for six years.

Only long experience can give exact information as to what premiums patients with gastric ulcer should pay for insurance. From the statistics presented, it would seem obvious that no one over thirty years of age should ever be accepted when the symptoms have been of short duration and when a "cure" has been but recently accomplished.

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CHRONIC DUODENAL STASIS OBSERVATIONS IN TWENTY-FOUR CASES.*

By Julius Friedenwald, M.D.,
PROFESSOR OF GASTROENTEROLOGY,

Theodore H. Morrison, M.D.,
ASSOCIATE PROFESSOR OF GASTROENTEROLOGY,

AND

Maurice Feldman, M.D.,
ASSISTANT PROFESSOR OF GASTROENTEROLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND, BALTIMORE, MD.

(From the Gastroenterological Clinic of the Department of Medicine of the University of Maryland.)

Although chronic dilatation of the duodenum has long been recognized, it is only within recent years, that any actual clinical significance has been attached to this affection. Aside from congenital factors, the following conditions favor its formation; adhesions, compression of the duodenum and prolapse of the colon into the pelvis. Adhesions ordinarily involve the first and second portions of the duodenum. Especially important in this direction are the obstructions produced as the result of adhesive processes due to intraduodenal lesions, as ulcer or tumor; chronic cholecystitis; adhesions between the duodenum and hepatic flexure and those formed as the result of visceroptosis or following abdominal operative procedures. Pressure on the duodenum occasioning duodenal stenosis may result from spinal deformities and also from growths involving abdominal organs such as the pancreas and from pressure

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due to ptosis of the right kidney. It is of importance to note, however, that according to Bloom and Arens as well as others, that inasmuch as chronic duodenal stasis is observed so frequently intimately associated with other affections, it should not be considered as a distinct clinical entity, but only as a radiologic phenomenon the result of such lesions. This view has not been accepted by most authorities.

Incidence. Chronic duodenal stenosis may occur at any age. The youngest case reported is that of three years, the oldest of sixty-six years. The highest incidence of this affection occurs during middle life, that is between thirty and forty years.

Of the 24 cases of chronic duodenal stasis in our series, 18 were males and 6 females. It is maintained by most authorities that this affection occurs twice as frequently in females as males which is contrary to the findings in our cases.

TABLE I.—CASES ARRANGED ACCORDING TO AGE AND SEX.

Age (years).	Males.	Females.
20 to 30	2	1
30 to 40	10	4
40 to 50	4	1
50 to 60	2	0
Total	18	6

Symptomatology. The symptoms of chronic duodenal stasis, according to our experience, are not always characteristic, especially in mild forms. In these cases, there are often periodic attacks of nausea and vomiting so-called bilious attacks which may have occurred over a period of many years, often since childhood. These are frequently preceded by intense constipation and are often accompanied with headaches and migraine attacks. The constipation is occasionally replaced by intermittent outbreaks of diarrhea. Attacks of nausea and vomiting occurred in 18 of our cases; migraine attacks in 15; constipation in 19; intermittent diarrhea in 3. Pain may be absent, mild or severe and may present no special relation to food. This symptom occurred in 16 of our cases; in 9 of which it was mild and in 7 severe. Changes in posture may in some instances afford relief from this symptom. Occasionally, the liver enlarges with an attack and tenderness may occur at this time under the right costal arch. Tenderness under the right costal arch with enlargement of the liver was noted in 5 of our cases. Due to the frequency of these attacks, loss of weight and strength is not unusual and neurasthenic symptoms are apt to supervene. During the interval of freedom from these attacks which may extend over a period of some days, the patient may enjoy comparatively good health. While in the milder intermittent type associated with infrequent attacks the pylorus retains its normal tonicity and

regurgitation takes place only when the obstruction permits an excessive amount of duodenal contents to accumulate. In the more chronic and severe forms, the pylorus becomes patent and dilatation of the stomach may occur. In many of these cases the pylorus remains constantly open and is greatly increased in diameter, often to such a degree that nausea and vomiting of bilious contents becomes more or less persistent and even vomiting of the retention type may occur, as was noted in 2 of our cases. The patient may complain of fullness, heaviness and distention and of eructations of gas following meals and not infrequently of pain which may extend over the entire abdomen or be limited to the epigastrium, or right upper or lower quadrants of the abdomen. Headaches become incessant and migraine attacks with bilious vomiting, malaise, faintness and dragging sensations are not infrequent. Occasionally an urticarial eruption is observed; this occurred in one of our cases. The symptoms vary somewhat according to the location of the obstruction. When obstruction occurs at the first part of the duodenum, the symptoms largely resemble those of pyloric stenosis. In other instances, pain extending over the gall-bladder region with enlargement of the liver and jaundice may erroneously give rise to the diagnosis of cholecystitis. This error occurred in 2 of our cases. In still others, pain may occur several hours following meals together with symptoms of hyperacidity and consequently an incorrect diagnosis of ulcer may be made, as was noted in 3 of our cases. Occasionally the attacks may disappear for periods of months or even years during which the patient may enjoy good health, when a relapse may occur following an acute illness, such as grippe. The discomfort and pain which is usually present in these cases during an attack and which is frequently aggravated in the recumbent posture may be relieved at times by elevating the pelvis or having the patient assume the knee-chest posture. These procedures were of distinct advantage in overcoming attacks in many of our cases. In the very aggravated types with gastric retention and profuse bilious vomiting a high degree of toxemia may occur. This may be associated with marked dehydration, shock and at times with attacks of tetany.

Among the associated conditions noted, peptic ulcer is most important. Gastric ulcer occurred in three of our cases; an esophageal diverticulum in one, mucous colitis in three and cholecystitis in one.

Case History. The following history presents the most important features of a typical case. D. B. F., male, aged forty-three years, had been complaining of indigestion for many years, consisting of attacks of pain in the upper right quadrant, with discomfort in that region running into the back toward the right shoulder blade. In the spring of 1909 these attacks became more severe and frequent, and the diagnosis of cholecystitis was made and a cholecystostomy was performed. No stones were found but the diagnosis of chronic cholecystitis was confirmed.

The patient remained well for a number of years but within the last two or three years had frequent attacks of nausea and vomiting. The vomitus recently contained food ingested several days previous. With this, there has been considerable discomfort in the upper right quadrant; headaches; fullness and distention after eating and gaseous eructations. The patient, in consequence, has been forced to live on a restricted diet. He is very constipated and has lost about 10 pounds in weight.

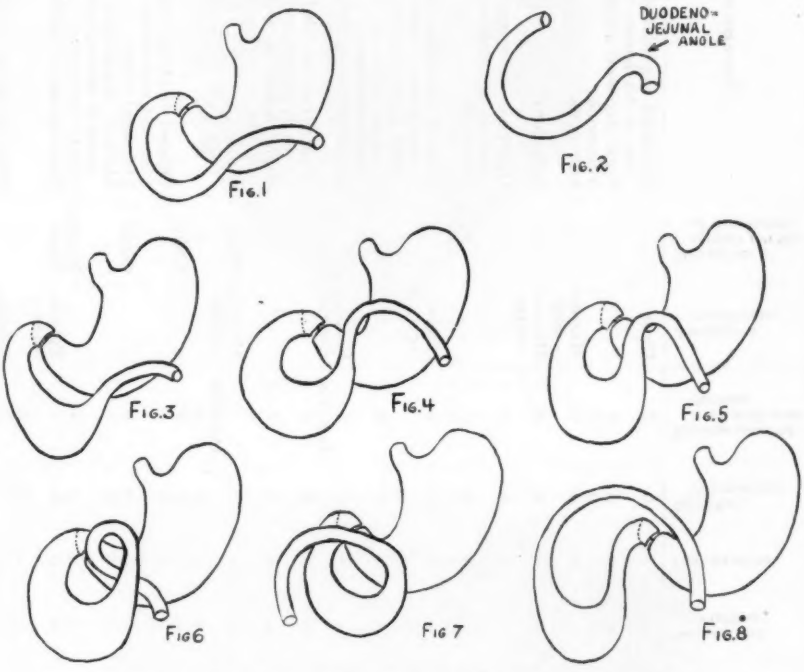

FIG. 1.—Schematic drawings; Fig. 1 illustrates the normal duodenal curve with relation to stomach; Fig. 2, normal duodenal curve. Fig. 3, shows a sagging of the duodenum with normal duodenal curve. Figs. 4, 5, 6, 7, 8, shows a sagging of the duodenum, with interference of the normal duodenal curve, resulting in stasis.

On examination, the chest organs were found normal. The abdomen was slightly distended, but there were no enlargements, masses, or peristaltic waves present and there was distinct tenderness under the right costal arch. The test meal showed a total acidity of 18 with the absence of free hydrochloric acid but contained considerable mucus. A meal given at night and extracted the following morning, disclosed considerable retention. The Roentgen ray examination was as follows: The position of the stomach is normal. There are no filling defects present. The duodenal cap is dilated but regular in outline. The second portion is markedly dilated, showing a distinct retention and constriction at its distal portion. A sacculation, about the size of a dime is also observed, projecting from the inner aspect of the second portion of the duodenum, which suggests the ampulla of Vater. The colon is in normal position. The diagnosis of the duodenal stasis with definite retention was made, which was confirmed by subsequent examinations.

TABLE II.—IMPORTANT FINDINGS OF 24 CASES OF DUODENAL STASIS.

Name.	Sex.	Age.	Pain.	Migrainous attacks.	Nausea and vomiting.	Constipation.	Diarrhea, intermittent.	Enlargement of liver with tenderness.	Associated conditions.	Dilatation of second portion of duodenum.	Roentgen ray findings.
1. H. V. U.	M	41	+	+	+	+	0	0	Ulcer	....	Duodenal cap dilated, stasis in second portion of duodenum, pyloric ulcer.
2. S. D. F.	M	59	0	0	0	0	0	0	....	....	Slight duodenal stasis, second portion.
3. H. P. N.	M	34	+	+	+	+	0	0	....	+	Adhesions.
4. H. F. W.	M	29	+	0	+	0	+	0	Mucous colitis	+	Adhesions.
5. E. L.	M	39	+	+	+	+	0	0	Mucous colitis	+	Adhesions.
6. B. S.	M	43	+	0	+	+	0	+	....	....	Duodenal stasis; gastric retention, second portion of duodenum irregular.
7. S. L. P.	M	36	+	0	0	+	0	0	....	+	Adhesions.
8. T. B.	M	56	0	+	+	+	0	0	....	+	
9. D. H.	F	38	+	+	+	+	0	0	Cholecystitis	....	Marked dilatation of duodenal cap, with slight gastric retention, result of extensive right upper quadrant adhesions.
10. A. H. W.	M	38	0	+	+	+	0	0	....	....	Constriction in upper jejunum, resulting in duodenal stasis.
11. L. A.	F	37	+	+	+	+	+	+ Jaundice	Esoph. divertic.	....	Duodenal stasis, second portion.
12. A. D. M.	M	37	+	+	+	0	0	0	....	....	Constriction in third portion of duodenum with dilatation and dilated duodenal cap.
13. R. J. S.	M	32	0	+	+	+	0	0	....	....	Slight stasis in second portion of duodenum.
14. S. R.	F	35	+	0	0	+	0	+ Jaundice	Mucous colitis	Slight	
15. T. G. O.	M	32	0	+	+	+	0	0	....	+	
16. B. J. T.	M	31	+	+	+	+	0	0	....	Slight	
17. B. C. H.	M	37	+	+	+	+	0	+	....	....	Dilated duodenal cap, duodenal stasis with marked angulation of third portion.
18. T. H. L.	F	46	0	0	0	+	0	0	....	Slight	Duodenal stasis.
19. M. O.	F	26	+	+	+	+	0	0	....	....	Marked angulation of duodenum with stasis in second portion.
20. D. B. F.	M	43	0	+	+	+	+	+	....	Marked	Gastric retention.
21. M. T. A.	M	34	+	0	0	0	0	0	Pyloric ulcer	Slight	Stasis in second portion.
22. O. R.	M	26	0	0	+	+	0	0	....	+	
23. G. F. L.	M	47	+	+	+	0	0	0	Gastric ulcer	+	Stasis in second portion.
24. S. H.	F	33	+	0	0	+	0	0	....	+	

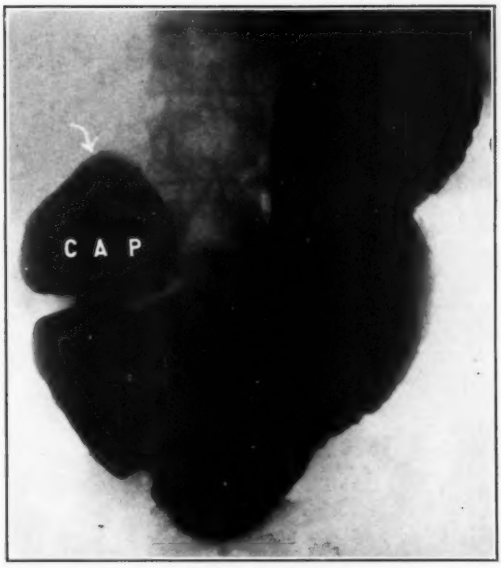

FIG. 2.—Shows a dilated duodenal cap forty-five minutes after a barium meal. No barium observed beyond the cap.

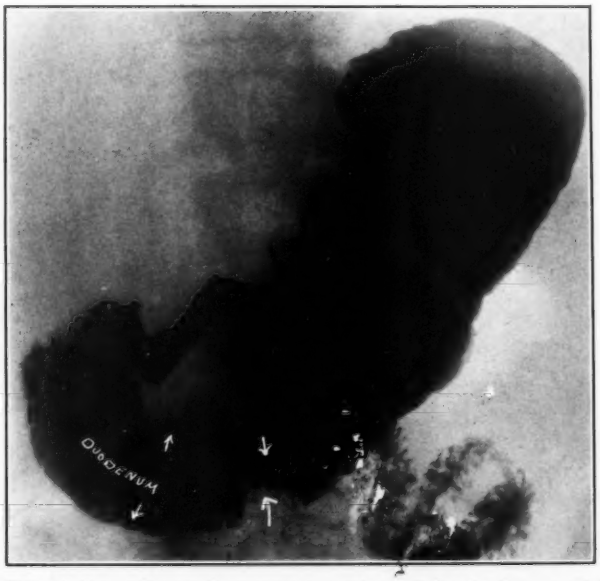

FIG. 3.—Dilated descending and transverse portions of the duodenum, with a constriction at junction with ascending portion.

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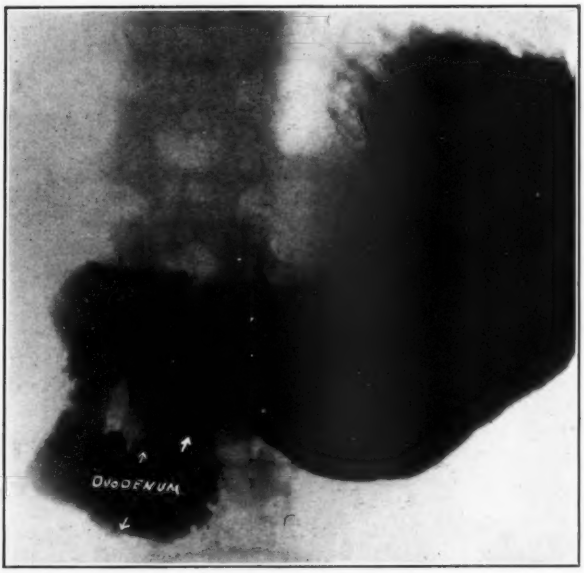

FIG. 4.—Lagging of barium in transverse portion of duodenum forty-five minutes after a barium meal; no barium observed beyond this portion.

FIG 5.—Lagging of barium in transverse portion of duodenum; the meal continues to pass on into the small bowel.

FIG. 6.—Constriction in jejunum, causing stasis; no barium beyond constricted area after one hour.

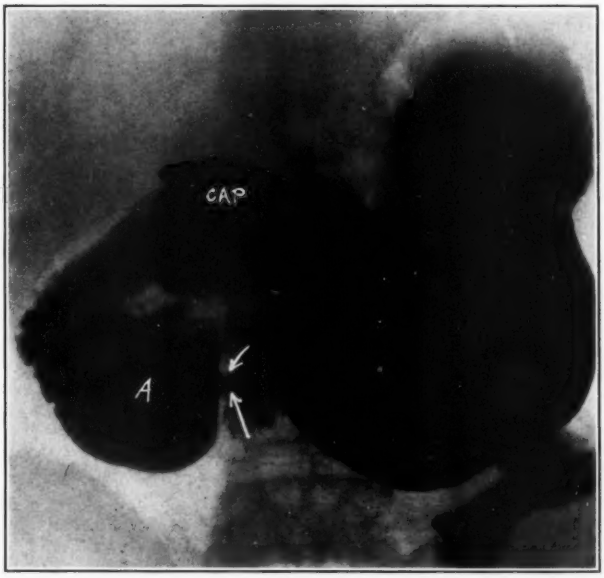

FIG. 7.—Illustrates marked dilatation of duodenum, resulting in partial obstruction; arrows point to constriction.

Diagnosis. The patient is usually observed to be slender of the asthenic type, presenting the narrow costal angle usually observed in visceroptosis. The stomach and colon are prolapsed and atonic and a succussion sound is readily elicited over the gastric area. Tenderness is ordinarily noted in the epigastrium or to the right or left of the umbilicus and an epigastric protuberance is occasionally observed. At times there is a general abdominal distention and the duodenal dilatation may be so marked as to present the sensation of a tumor mass to the palpating hand. This mass may be tympanitic or a succussion sound may be elicited from it and pressure over it may produce nausea.

In the milder type the gastric acidity is usually normal. Occasionally hypochlorhydria or hyperchlorhydria may occur. In the more severe forms, due to the admixture of large quantities of bile, achylia is usually present. The gastric contents may present all of the characteristics observed in pyloric stenosis, containing remains of food ingested on the previous day together with an admixture of dark-green bile and much mucus.

Of our 24 cases, the gastric acidity was normal in 13 instances; hyperchlorhydria was present in 7 instances and hypochlorhydria and achylia in 4.

While the diagnosis is made possible in rare instances from the history and physical findings alone, the Roentgen ray evidence is far more conclusive. The Roentgen ray signs of this affection are well defined and extremely characteristic and a certain diagnosis can only be made by means of this procedure. The Roentgen ray findings are based largely upon fluoroscopic examinations by means of which changes in motility can be carefully observed. The films, however, record the definite anatomic changes. The fluoroscopic examination is usually most satisfactorily made with the patient in the upright posture when viewed semilaterally with the right side nearest the screen. However, the obstruction can ordinarily also be well observed when the patient is recumbent and satisfactory films may be obtained in either position. Delay in the barium meal is not infrequently overcome by change in posture of the patient which can readily be observed under the screen. When an accumulation of barium occurs in the duodenum at any point, the mass is divided and passes in opposite directions along this organ. Retention in the duodenum can be considered positive when the barium is retained longer than a period necessary to complete the passage of two gastric peristaltic waves. In the more marked cases, however, gastric as well as duodenal six-hour residues of the barium are not uncommon.

The dilated duodenum can frequently be most satisfactorily observed from one to two hours following the barium meal. At times evidence of antiperistalsis with regurgitation of the barium meal into the stomach are noted fluoroscopically. In order to

eliminate the presence of duodenal stasis, the duodenum must be observed at intervals over a period of at least thirty to forty minutes. The presence of this condition is suggested when the duodenum is constantly visible during the period of emptying of the stomach.

In stenosis, between the first and second portions of the duodenum, the duodenal bulb may be elongated, dilated and will present evidence of delay in the expulsion of the barium. The first portion may also be distorted giving rise occasionally to the appearances noted in ulcer. In some instances, visualization of the third portion of the duodenum may be obscured, due to an enteroptosis, and lateral views must then also be obtained. The stomach is usually prolapsed in these instances, and may present a six-hour as well as an eighteen-hour retention. In these cases the barium passes without difficulty through the first part of the duodenum to the transverse portion where it remains stationary. At this point, violent peristaltic movements (the so-called writhing duodenum) are noted as if the barium were forcing its passage through some obstruction, when reverse peristalsis suddenly takes place and the barium is carried back into the duodenal bulb. These phases are rapidly repeated and after a certain delay portions of the barium are forced through the area of obstruction into the jejunum. Above the area of apparent obstruction dilatation of the duodenum is noted.

Obstruction of the second portion of the duodenum is usually more readily visualized. A rather characteristic picture is observed four to five hours following the barium meal in the form of a saucer-shaped residue in the second and third portions of the duodenum. The duodenum may be dislodged downward or it may present itself forward, being freely movable in the abdomen. Obstruction of the fourth portion of the duodenum is usually easily visualized. Stasis occurred in most of our cases in the second and third portion, the most frequent site being in the second portion. In one instance, it occurred in the upper jejunum, resulting in duodenal stasis.

Finally, in considering the diagnosis it should be recognized that duodenal stasis is not a rare condition and that it is not infrequently overlooked. In some instances, in fact, the affection may continue on for long periods without presenting symptoms. It is always important, however, in order to be certain that the stasis is permanent that repeated Roentgen ray examinations be made. Repeated examinations were made in all the cases in our series. Inasmuch as headaches associated with nausea and vomiting are frequently present, the diagnosis of migraine is not uncommonly made. It is, therefore, important in all obscure forms of migrainous headache that thorough roentgenologic studies of the duodenum be made. In some instances, the symptoms are attributed to gall-bladder disease, ulcer or even to neurasthenia.

As the clinical history of the affection is often indefinite, certain characteristics should be held in mind. Occasionally, there will be

single attacks following meals of but a few days duration, disappearing for a variable period of time and again recurring. At other times, the attacks may occur daily, following one or other of the meals. It is important to note that the attacks may have their onset in childhood and yet the condition not be recognized until later in life when the symptoms become sufficiently urgent to demand thorough investigation. In many instances the attacks appear suddenly following relaxation of the abdominal organs as after serious debilitating diseases or pregnancy, though even in these instances minor or fleeting attacks may have manifested themselves at times for long periods, the true nature of which may have remained unrecognized.

Treatment. In many instances, medical management is quite satisfactory and with conservative and postural treatment marked improvement frequently takes place. This is ordinarily observed in the milder types in which the symptoms occur intermittently and are followed by periods of relief. The cases due to visceroptosis are especially amenable to medical treatment.

Diet plays an important rôle in the management of these cases. This should be bland and of a high caloric value. Forced feeding and absolute rest in bed of from four to six weeks together with postural treatment is often indicated. Duodenal lavage through the Rehfuss tube is frequently of great benefit.

When the symptoms are severe or when adequate medical treatment no longer suffices in affording relief, surgical intervention is indicated; the most satisfactory procedure in most instances being duodenojejunostomy. When performing this operation, it is most important to undertake a complete investigation of the abdominal viscera, so that all complications may as far as possible be corrected during the time of this procedure. If the gall bladder is found diseased or when a peptic ulcer is detected or dilatation of the stomach exists, the procedures ordinarily undertaken for relief of these conditions should be carried out. When the duodenal stenosis is caused by adhesions, these should be released and if the duodenum is found markedly dilated and atonic a duodenojejunostomy should be performed.

The more radical measures, as extensive resections of the colon when coloptosis is present as a complicating factor, rarely warrant their extreme risk. Suspension of ptosed viscera is likewise ordinarily unsuccessful in its results.

Of our 24 cases on which this study is based, 23 were treated by means of the medical measures already referred to, with at least satisfactory temporary relief. In a single instance, which resisted this form of treatment, duodenojejunostomy was followed by complete recovery.

Summary. An analysis of 24 cases of chronic duodenal stasis leads to the following conclusions:

The condition is made possible both by anatomic and embryologic factors, and by conditions favoring adhesions or pressure on the duodenum due to spinal deformities or growths in the abdomen or traction on the mesentery due to visceroptosis.

In some instances, no demonstrable lesion has been ascertained; in the more chronic forms however, the pylorus is patent and there is permanent dilatation of the first three portions of the duodenum. Duodenal stenosis may occur at any age, though the greatest incidence is during middle life. According to most authorities, it occurs twice as frequently in females as in males.

The symptoms are not always characteristic, especially in the milder forms. There are periodic attacks of nausea and vomiting, so-called bilious attacks. There is often constipation with intermittent outbreaks of diarrhea. Change in posture may afford relief of symptoms. Loss of weight and strength is not unusual and neurasthenic manifestations are common. During the interval of freedom from attacks, the patient ordinarily enjoys good health. As the disease becomes more chronic the dilatation extends into the stomach, when nausea and vomiting become persistent. Headaches and migraine attacks are not infrequent. In the more aggravated types a high degree of toxemia may develop.

As associated conditions, a number of instances of peptic ulcer have been recorded. Gastric dilatation of varying degrees is not uncommon. Cholecystitis and pancreatitis occur due to an ascending infection.

In the diagnosis the presence of visceroptosis is important. The only conclusive evidence of this condition can be obtained by means of the Roentgen ray which reveals a delay or retention of the barium in the dilated duodenum.

In many instances, medical management is quite satisfactory especially in those instances due to visceroptosis. In the severe types accompanied by excessive vomiting and dehydration with a threatened alkalosis, the intravenous administration of sodium chloride solution with glucose is indicated. When the symptoms are severe or when adequate medical treatment no longer suffices in affording relief; surgical intervention is indicated, the most satisfactory procedure being duodenojejunostomy.

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THE EFFECT OF INTRAVENOUS INJECTIONS OF VARIOUS EMULSIONS OF FAT ON THE EMPTYING OF THE GALL BLADDER.*

By George M. Higgins, Ph.D.,

and

Charles M. Wilhelmj, M.D.,

division of experimental surgery and pathology, the mayo foundation, rochester, minn.

Investigators in the field of gastrointestinal physiology are agreed that the ingestion of food rich in fat causes more or less complete evacuation of the gall bladder. Furthermore, there is

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general agreement in the conclusion that this evacuation, more extensive in certain species of animals than in others, is effected by the active contraction of an intrinsic musculature within the tunic of the gall bladder. This conclusion, which was reached independently by at least three groups of workers and supported by adequate experimental evidence, largely minimizes the earlier recorded observations that extrinsic factors, such as secretory pressure or intraäbdominal pressure, were primary in their effect on the flow of bile from the gall bladder. Whitaker,[12] in commenting on the mechanism of the gall bladder, concluded that extrinsic factors do not have an appreciable influence, but that emptying of the vesicle is produced primarily by contraction of the muscle layer. He further concluded that contraction is probably not dependent on a reflex nervous mechanism, and that the evidence is not conclusive that hormone action is the exciting factor.

Egg yolk and cream, first used by Boyden[1] in experimental studies on the gall bladder, is perhaps the diet most effective in emptying the viscus. Since Boyden's significant observation, Whitaker has shown that emptying of the gall bladder could likewise be produced in cats by the ingestion of other fats. Subsequently, Krause and Whitaker[9] reported their observations on the gall bladders of cats following the ingestion of various food substances, such as olive oil, cod-liver oil, cocoanut oil, and certain carbohydrates, as well as protein substances. They concluded that fats and fatty acids are by far the most active in emptying the gall bladder, that carbohydrates are practically ineffective, and that pure proteins produce but slight emptying of the viscus.

Boyden[2] concluded that the gall bladder may be a trigger mechanism, set off by a number of foods, but that the degree or extent of emptying will depend on the time the digesting food is withheld in the stomach. Boyden and Saunders[5] further showed that when food is placed directly into the duodenum the extent of contraction of the gall bladder is not lessened. Higgins[7] observed that when food is introduced directly into the duodenum of a fish, sustained contraction of the gall bladder was not induced for periods ranging from an hour to an hour and a half. The initial stimulus of the food on the duodenal mucosa did not have any appreciable effect on the biliary vesicle, and it was not until considerable absorption had occurred and the residual food content had reached the lower intestines that the gall bladder contracted. In these observations on the fish, it must be recalled that laparotomy was done so that observations were made on the exposed viscera, a procedure which may or may not explain the prolonged interval between the feeding and the contraction of the viscus.

Fatty foods, however, are not the only substances that cause partial or complete evacuation of the gall bladder. Magnesium sulphate, when injected directly into the duodenum of man, causes

an expulsion of bile from the gall bladder induced by active contraction.[5] Subsequently, it has been shown that magnesium chlorid and sodium sulphate in strong solutions cause as effective a discharge of bile from the gall bladder of human beings as magnesium sulphate.[4] This is true whether these salts are administered by mouth or introduced by a Rehfuss tube. Although marked intestinal peristalsis has been induced in experimental animals by these salts, yet failure of the animal's gall bladder to contract casts considerable doubt on the validity of earlier observations that peristalsis of the gastrointestinal tract induces the organ to empty.

Besides these salts, certain acids have been shown to induce the flow of bile from the gall bladder. It has been known for a long time that a few drops of a weak solution of hydrochloric acid will cause bile to flow from the biliary duct system. Elman and McMaster[6] demonstrated that relaxation of the mechanism of the sphincter at the end of the common bile duct could be induced by a tenth-normal solution of hydrochloric acid. Boyden and Birch[3] were not able to secure as effective a discharge of bile from the common duct following lavage with hydrochloric acid as they did following the drinking of a glass of water. On the other hand, Ivy and Oldberg[8] were able to induce contraction of the gall bladder in animals by the introduction into the duodenum of 20 to 30 cc. of tenth-normal hydrochloric acid. Subsequently, these authors, from studies on cross-circulation experiments, concluded that hydrochloric acid given into the duodenum to one animal may induce the contraction of the gall bladder of the second animal within ten minutes. Some action of an hormonic nature incited within the duodenum of the first dog becomes effective by passage through the blood stream into the second animal.

In addition to the mechanism set up within the gall bladder either by nervous stimulation or by hormonic activity, a regulatory mechanism guards the portal of the common duct into the duodenum. The literature on the sphincter of Oddi, its physiology and anatomy, and its presence or absence, is enormous, and no attempt will be made to review it here. It is sufficient to state that the best authorities on the physiology of the extrahepatic biliary tract are rather agreed in affirming the existence of some regulatory mechanism at the duodenal end of the common bile duct which functions in a way to regulate largely the filling and emptying of the gall bladder.

Method of Study. Although the gall bladder is known to react to various saline cathartics, acids and even to mechanical disturbances, its essential physiologic rôle seems in some way correlated with metabolism of fat. Since we have observed the emptying of the gall bladder in animals in which the duodenum had been experimentally isolated from the gastrointestinal tract, we believe that at least the duodenal mucosa did not play an essential part in causing the con-

traction of the viscus. Sosman, Whitaker and Edson[11] had shown that in cases of pyloric resection and gastrojejunostomy the gall bladder emptied as well after eating as in the normal subject. It has seemed to us that the amount of bile discharged from the gall bladder has appeared to be in some way correlated with the absorption of fat. Krause and Whitaker[9] had observed in their study of the effect of various foods that "the degree of absorption of fat is probably related to the degree of the emptying of the gall bladder." Whether the degree of contraction of the vesicle is dependent on the extent of absorption cannot be stated. More than likely the gall bladder bile facilitates digestion, thus securing greater absorption. In a recent study of the relation of the emptying of the gall bladder to the digestion of fats, Silverman, Denis and Weinberger[10] concluded that such emptying is not dependent on the absorption of the fat, so far as can be determined by analysis of the blood for fat.

We were prompted to try a series of experiments in which various highly emulsified fats were injected directly into the blood stream. Whitaker[12,13] has described the intravenous use of an olive-oil emulsion which was followed by the emptying of the gall bladder. He also showed that an intravenous injection of liquid petrolatum was nearly as effective as olive oil in this respect. For some time one of us (Wilhelmj) has been conducting a series of observations on the metabolism of fats following both oral and intravenous administration. Since the slow intravenous injection of various fat emulsions causes a definite increase in basal metabolism, we were interested to know whether any response could be incited within the gall bladder by the intravenous injection of these emulsions. There would, perhaps, be no occasion for the discharge of gall bladder bile since the gastrointestinal tract was inactive; and yet if the contraction of the viscus was due to an absorbed fatty constituent acting through the blood stream, then a response could, perhaps, be induced by the presence of the fat in the emulsified or the digested state within the blood stream. In these observations, we have used emulsions differing somewhat from that employed by Whitaker. In most of the experiments we have used highly emulsified olive oil or dog lard, the latter obtained by rendering dog fat. These two fats were emulsified in three different types of mediums: 5 per cent gum-acacia solution, 2 per cent aqueous lecithin solution and autogenous blood serum. These emulsions were prepared with and without the bile salt, sodium glycocholate (Merck), known to be without effect on the gall bladder. When the sodium glycocholate was used, it was administered in amounts equal to 0.05 gm. for each kilogram of body weight. Accordingly, six different emulsions were employed in the study and the quantities of fat varied, ranging in volumes equivalent to 0.5, 1 and 2 gm. for each kilogram of body weight. In a few experiments the dog fat was partially digested,

previous to its use, by an alcoholic extract of canine pancreas. Several observations also were made on animals following the intravenous injection of an emulsified preparation of egg yolk and cream.

The detailed method of preparation of these emulsions will be given in a future paper and only the general procedure outlined here. A weighed amount of melted dog lard or olive oil was poured into the emulsifying medium which had previously been warmed except in the case of blood serum which was used without warming. The mixture was then put into a mechanical shaker for thirty minutes to one hour. At the end of this time the emulsion was put into a small separatory funnel and allowed to stand ten minutes and then separated from the excess water which rises to the surface. When sodium glycocholate was used it was dissolved in 3 to 5 cc. of water, heated, and then added to the fat or olive oil with constant vigorous stirring, so that a homogeneous mixture was obtained; following this the emulsion was prepared as usual. When partially digested fat was employed, an alcoholic extract of canine pancreas was added to the fat and bile-salt mixture and digested for about twenty-four hours at 70° C. The alcohol was removed by aëration and the emulsion prepared, as has been outlined. The emulsions of egg yolk and cream were prepared by thoroughly mixing the egg yolk and cream, shaking for about ten minutes, centrifugalizing and employing the upper portion of the mixture. The emulsions prepared in blood serum and 2 per cent lecithin are the most satisfactory from the physical standpoint. Fat emulsified in 2 per cent lecithin with or without sodium glycocholate is in a very fine state of division; the particles are much smaller than erythrocytes and show active Brownian movement.

When the preparations are properly made and completely emulsified, the animal is not disturbed when the emulsions are slowly injected into the jugular or saphenous vein. Occasionally too rapid injection may result in increased respiration, accompanied by slight movements. Ordinarily, if the injections are made slowly over a period of eight to fifteen minutes, the animal is not inconvenienced. Fifteen dogs and fifteen cats comprised the series of animals used in this study. Three methods are employed: the lipiodol method used by Whitaker and Boyden, the common duct intubation, and the direct observation. The first of these is perhaps the best in that it permits the recognition of degrees of emptying and slight tonic changes.

Experimental Observations. The dog-fat bile-salt acacia emulsion was given to three dogs. Under ether anesthesia, the bile was withdrawn from the gall bladder of two of these and lipiodol was injected in its place. The common duct in the third dog of the series was intubated and the rubber catheter brought to the exterior through a small stab wound. The dogs were fasted twenty-four hours follow-

ing the surgical preparation, when cholecystograms of the dogs that had been given lipiodol still showed well-filled gall bladders. The emulsion, containing 1.5 gm. of dog fat for each kilogram of body weight, was then slowly injected into the jugular vein over a period of fifteen minutes. Cholecystograms were made 5, 15, 30, 60 and 90 minutes after the injection. Slight tonic changes were periodically visible over the gall bladder during this period. Slight changes in shape or contour were noted and yet lipiodol was never visible in the cystic or common ducts. These slight tonic changes, rhythmically appearing, have been frequently noted and probably do not bear any relation to the injected emulsion. Following the intubation of the common bile duct in the third dog of the series, samples of bile were collected every five minutes for one hour. The emulsion, comparable in fat content to that mentioned, was injected slowly into the jugular vein over a period of fifteen minutes, during which time the animal remained quiet. Samples of bile collected before and during the injection were comparable both in volume and in concentration of pigment. Toward the close of the injection a slight increase in concentration suggested the discharge of gall bladder bile, but in quantities so slight as to be insignificant. Following the injection, five-minute samples of bile likewise compared favorably both in volume and concentration with those taken prior to giving the emulsion, and one must conclude that the intravenous fat injection is without significant effect on the gall bladder.

Intravenous injections of olive-oil emulsions to which was added 0.05 gm. of sodium glycocholate for each kilogram of body weight were given to six dogs. Four of the dogs had been prepared for cholecystographic studies by the lipiodol injection, one had a common bile-duct intubation, and the gall bladder of the sixth was observed directly following the intravenous injection of the emulsion. Cholecystograms taken at successive intervals following injection did not reveal appreciable change in the contour of the gall bladder. Slight changes in shape are visible, but these do not bear any relation to the emptying of the vesicle, for lipiodol was not visible in the cystic or common ducts. A cholecystogram taken one hour following egg yolk and cream by mouth shows the vesicle nearly empty. Bile collections from the intubated common duct of the animals of this series were not appreciably changed following the injection of the emulsion. For two hours preceding the injection, five-minute samples averaged 2 cc. of clear amber bile. During the injection and for twenty minutes thereafter, bile ceased to flow; then gradually there was a return to the average volume. Collections were continued for two and a half hours following the injection, but there was no indication that bile had been expelled from the gall bladder.

Three dogs were tested, following preliminary preparation with lipiodol, with the dog fat emulsified with a 2 per cent aqueous lecithin solution. The emulsified dog fat, partially digested with an alcoholic pancreatic extract, was given to one of these three dogs. In these animals, either with or without the addition of the pancreatic extract, we were unable to recognize any marked changes in the gall bladder following intravenous injection of the emulsions. Subsequent oral administration of egg yolk and cream, however, was effective.

A single experiment was tried by using an emulsion of pure olive oil, and in this, as in all others of our series, the gall bladder did not empty. A single observation was also made on a dog that was given an emulsion of dog fat, which had been subjected to the digestive action of an alcoholic pancreatic extract, and to which a known quantity of sodium glycocholate was added. Slight tonic changes only were visible but lipiodol did not enter the cystic duct.

In the fifteen cats used for this study only two had been prepared previously for cholecystograms by the injection of lipiodol. All others were explored at successive intervals following injection and direct observations were made on the gall bladder. The direct observation has certain advantages in that one may see at a glance the actual state of collapse of the vesicle, and may actually locate the bile expelled. On the other hand, slight changes cannot easily be recognized. However, we were not concerned with qualitative reactions or with degrees of emptying; we rather wished to know whether the gall bladder would expel any bile when fat is introduced into the blood stream. Accordingly, the necropsy method proved entirely satisfactory for our purpose.

The cats previously prepared by the injection of lipiodol were given 3.7 cc. for each kilogram of the olive-oil sodium-glycocholate emulsion through the saphenous vein. Cholecystograms made at 5, 15, 30 and 90 minutes showed slight tonic changes manifested by changes in the shape of the vesicle, but lipiodol was never forced out into the ducts. That the duct system was patent and physiologically functional is shown by the fact that a cholecystogram taken one hour after feeding egg yolk and cream showed a contracted gall bladder with the oil distending both cystic and common ducts.

Resort was then had to the necropsy method. A series of cats was given intravenous injections of emulsions of both olive oil and dog fat in lecithin or serum, to which was added, in either case, a known volume of bile salts. Injections were again slowly made through the saphenous vein, over periods ranging from five to eight minutes. The animals were killed at successive intervals, up to an hour following the injection, and the gall bladder and gastrointestinal tract were immediately explored. Prior to injection the animals were fasted for eighteen hours, so that the vesicles should be well

distended at the time of injection. Necropsy data, following intravenous injection of either emulsion, invariably revealed a well-distended gall bladder containing heavily concentrated bile. Observation of the contents of the gastrointestinal tract from pylorus to ileocecal valve did not disclose evidence of gall bladder bile, and the conculsions were manifest that the gall bladders had not emptied following the intravenous injection of fat.

To determine whether or not the emulsion we were using could cause the discharge of gall bladder bile when given orally, we arranged to feed a similar series of cats with emulsified fats like those given intravenously. Accordingly, the fats were prepared in a similar manner, and quantities proportionate to those given intravenously were given by mouth. In some cases the stomach tube was passed, and in others the animal was given the emulsion through the angle of the mouth so that swallowing was normal. Here again the animals were killed at 5, 15, 30, 60 and 120 minutes after the feeding. Exploration showed in each case that the gall bladder had emptied, and in the longer periods it had emptied completely. An immediate response was apparently set up within the gall bladder, for in the animals explored within five minutes after feeding, the vesicle was partially empty and isolated spurts of gall bladder bile appeared in the duodenum. Exploration at 30, 60 and 120 minutes after food was given showed the gall bladders greatly contracted and concentrated bile at intervals throughout the gastrointestinal tract to the ileocecal valve. The occurrence of concentrated bile at different levels throughout the gastrointestinal tract suggests that the discharge from the vesicle had occurred in more or less rhythmic spurts and not as a continuous discharge.

Comment and Summary. These observations on the gall bladders of cats and dogs following the intravenous and oral administration of certain emulsions of fat show rather definitely that contraction of the gall bladder does not take place when these emulsions are injected directly into the blood stream. This is true whether or not the fats are partially digested prior to the injection.

This is at variance with the observations of Whitaker[12,13] following the intravenous injection of an emulsion of olive oil. We are at a loss to explain the disparity in our results. Both in cats and dogs, using either method of study, we were not able to conclude that active contraction of the vesicle occurred. Minor changes in contour, indicating tonic variations, were manifest, but lipiodol was not forced into the cystic duct by these changes. The fact that Whitaker also secured partial emptying following the intravenous injection of liquid petrolatum, a substance ordinarily without effect on the gall bladder, when given by mouth, suggests that perhaps factors other than the presence of the fat caused contraction following the intravenous injection of the olive oil. The physical organiza-

tion of the emulsions we employed may be the reason we were unable to secure contraction, and to substantiate Whitaker's observations.

This report covers a series of observations made on the gall bladders of cats and dogs which have received intravenously various emulsions of fat. The emulsions most extensively studied were olive oil and dog fat, in either autogenous serum or a 2 per cent lecithin solution. Emulsions were used either with or without a known quantity of sodium glycocholate. The injections were made slowly through the jugular or the saphenous vein, and the animal ordinarily remained quiet during the entire period. Studies of the gall bladder following the intravenous injection of these emulsions were made by the cholecystographic method following the injection of lipiodol, common-duct intubation, and the necropsy method. The results of these three methods of study are in agreement in that the gall bladders of cats and dogs do not empty when the emulsions of fat described are injected into the blood stream. Slight tonic changes which are noted are considered as insignificant and wholly unrelated to the presence of the fat. Observations made on the gall bladders of cats, following the oral administration of the emulsions described, show conclusively that the vesicle empties in response to these foods in the gastrointestinal tract, and, accordingly, the conclusions are manifest that contraction of the gall bladder is related to gastrointestinal activity either of a hormone or of nervous excitation.

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RUMINATION IN MAN.*

By Charles-Francis Long, A.B., M.D.,
PHILADELPHIA.

Human rumination has engaged the wonder of many clinicians for three hundred years. William Shakespeare was in his prime when an Italian anatomist, Jerome Fabricius of Aquapendenta,[1] set down the first record of this curious perversion of gastric and esophageal function. It concerned a young man who began to ruminate through worry because his father's forehead had sprouted horns. Fortunately for us, Fabricius became more concerned about the rumination than about the horns. Roughly a hundred years later, the famous de Peyer[2] devoted a large volume to Merycologia which is now only of historic interest. For any statistical needs our purpose is best served by the pithy contributions of Riesman,[3] Sinkler,[4] and Einhorn[5] in this country; Mueller,[6] Kohlmann[7] and Gulat-Wellenberg[8] in Germany; and Cambay[9] in France. The latter is important though he wrote almost a hundred years ago, because he was a physician and a ruminant.

The synonyms rumination and merycism mean "cud chewing," and are used by physicians to designate the similarity of these human actions to those of certain of the grass-eating animals. Even patients often comment about this. "Human Rumination is not an actual illness, but an ability to regurgitate a hastily eaten meal in large mouthfuls, to resalivate the food, chew it again and reswallow it. This procedure usually begins fifteen to thirty minutes after the meal, lasts from a half to one hour, and occurs fifteen to twenty times within this period. It stops automatically when food begins to taste sour."[7] It is then evidently an exact reversal of the normal—unchewed or very palatable food leaves the stomach, ascends the esophagus and is delivered into the mouth where it is either masticated or spat out. Only in very rare instances can it be either voluntarily started or stopped. There is never any nausea and no effort is necessary to bring the food up. In fact, food will often appear in the mouth despite a strong effort of the will to suppress the act. Most ruminants are hasty and large eaters and the size of the meal seems to have something to do with the return of the food and the length of time rumination will persist after eating.

The following patients have been seen during the last three years, most of them in the office of Dr. David Riesman, whose stimulation and courtesy have awakened my interest in this subject. They have been studied as thoroughly as the coöperation of

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the patient would permit, which will explain any evident omission of routine studies.

Case Reports.—Case I. Mr. J. C., aged fifty-five years, a real estate dealer of Russian-Jewish extraction, came in January, 1926, complaining that his food returned into his mouth. This had been going on for two years but had been worse for six months. It usually began fifteen to twenty minutes after every large meal, never after a light lunch, persisting for an hour to an hour and a half, the food coming sometimes in small amounts and sometimes in mouthfuls. The food always tasted the same as when first eaten, was never bitter, and he could recognize the various articles by their taste. He could not choose which food he would ruminate nor could he regurgitate at will. Even belching would not induce rumination. He was a very hasty eater with a voracious appetite, taking half a loaf of bread and three-quarters of a pound of beef at one meal, swallowed in large gulps practically unchewed. A few days before his visit he was able to take a large meal without ruminating by masticating properly. So far as he knew, there were no merycoles in his family nor had he seen anyone who ruminated. He was short and overweight, had ground down teeth, a lightly-coated tongue, tonsils cleanly removed. The abdomen was obese and tympanitic, otherwise negative. The epitrochlear glands were enlarged. Physical examination was otherwise negative.

Case II.—Mr. W. S., aged fifty-nine years, a Russian-Jewish tailor, has had regurgitation from eight to ten years, after heavy meals. It begins ten minutes after eating and recurs every two to three minutes for a half hour. The food tastes the same as when swallowed except coffee, which is usually sour. This man is not a fast eater nor a heavy one. He formerly chewed the regurgitated food and swallowed it; now, he often spits it out. He has no epigastric sensation of any kind while ruminating, he does not know why he may have originally begun to ruminate and neither of his parents and none of his children have this faculty. He cannot bring food up at will nor has he any selective power over the returned food. He is an undersized, spare individual—there is a good deal of "gold work" in his mouth, his abdomen is normal, and his reflexes normal. His gastric analysis shows free hydrochloric acid ranging from 10 in the fasting contents to 60 after an hour and a half, with a total acid of 95 at this time.

Case III.—A coal operator, W. A. S., aged sixty-five years, has been under observation since 1917, frequently seeking relief for belching, sour risings or flatulence, more recently for precordial distress and vertigo. In addition, to quote his own words, for three to four hours after a heavy meal "all my life food has returned into my mouth just as sweet as it went down." The food is reswallowed, he can bring it up at will and has at times brought it back to look at it. He always finds it unchanged, it has a normal taste, but he cannot select the food he desires. There is no familial nor imitative history. He is a wiry individual, well nourished, with diseased tonsils and a moderate amount of "gold work" in his mouth. There is a little cardiac enlargement, a mild hypertension, without evidence of decompensation. His abdomen is somewhat relaxed, the physique is otherwise normal. Since 1923 he has had a yearly gastric analysis, all showing an absence of free hydrochloric acid and a total acid ranging from 54 to 70. His gastro-intestinal tract has been Roentgen rayed three times. In 1922 and 1924 there was a marked pylorospasm with a slight retention at six hours. In 1928 the pylorospasm persisted, there were marked rugæ in the pyloric antrum and the duodenal cap gave the appearance as if there were a slight prolapse of gastric mucous membrane into it. The roentgenologist has

raised the question of gall bladder disease, but this cannot explain the rumination, for he states it has been present "all my life."

CASE IV.—In May, 1928, J. R., a Russian-Jewish Hebrew instructor, aged forty-two years, complained of indigestion which he said had been present for ten years. It began between the ages of twenty and thirty when, as a poor student, he could not get the proper food. An hour after his main meal "as regularly as clockwork" his food returns in mouthfuls without nausea and without discomfort in the epigastrium. It tastes the same as when eaten, it never becomes sour and may continue to return until the next meal. He says that being unable voluntarily to control rumination is often embarrassing to him when in company. Meats and fish in rich combination prove especially annoying and for this reason he has cut them out of his diet. There is no hereditary nor imitative history. He is a short, apprehensive individual, very well nourished, with a plate of false teeth above and a partial plate below. Except for infected tonsils his physical examination was entirely negative. Routine Roentgen examination of his stomach and esophagus showed no physical abnormality, though there was a slight amount of phrenospasm and a short initial pylorospasm.

CASE V.—T. R. C., aged sixty-three years, a physician of English birth, has been under observation for ten years, first complaining of hyperacidity and pain, which led to the diagnosis of duodenal ulcer for which he was surgically treated. A posterior gastroenterostomy was done by Dr. John Deaver in 1918. However, he remembers ruminating since the age of ten and has always chosen desserts, such as custard pie or fruit cake and especially marshmallow-flavored foods. He emphasizes the pleasure he derives from rumination and says that it amounts to doubling the enjoyment of a good dessert. In earlier life the food was returned within half an hour after eating and continued at intervals of two to three minutes until the food became sour. Of late years the interval of return has lengthened, now being between five and ten minutes. Formerly, he was able voluntarily to bring back desired food; now he ruminates occasionally unexpectedly. It has always been a source of embarrassment to him and he takes great pains to hide the procedure from others. For eight years preceding his first visit to our office he had periods of exacerbation of ulcer symptoms, during which he never ruminated, but the faculty would immediately return as soon as the dyspepsia disappeared. For two years following his operation he was unable to ruminate. Since then he has been able to do it with his old-time zest. He is short and wiry. He has almost an entire set of false teeth, scars of the abdominal operation, but is otherwise normal. Routine Roentgen ray of the upper gastrointestinal tract showed the stomach normal in size and shape, peristalsis good, and a gastroenterostomy opening on the greater curvature through which the barium passed freely. A small amount also passed through the pylorus.

CASE VI.—The most interesting case of this series is that of Hadji Ali, an actor. This performer, whom I have had the good fortune to observe, was born in Cairo, Egypt, and is now between thirty-five and forty years of age. He is short, stocky, exceedingly well-developed and well-nourished, with a tremendous abdominal musculature. Routine physical examination revealed no abnormality.

To being his act, he swallows fifty glasses of water, stands before a trough and without apparent effort brings the liquid up again. He then swallows thirty hazel nuts and an almond and brings up the number of hazel nuts stipulated by the audience before bringing up the almond. He then brings

FIG. 1.—Film of H. A. immediately after swallowing barium. Cardia and pylorus open, stomach and small intestine simultaneously filled. Film taken in recumbent posture.

FIG. 2.—Film of H. A. after voluntary emptying of the stomach. The small intestine is still completely outlined. The small barium shadow in the stomach is a residue pushed back from the intestine by the roentgenologist (see text). The linear shadow is a suspender buckle.

up the remainder of the nuts. Here, I believe the selection is done in the mouth. Next he swallows three handkerchiefs of different hues and brings them back singly in the rotation desired by the audience. I feel confident that these are flavored, enabling him to make selection in the mouth; however, he states that by long practice he has trained himself to stow the handkerchiefs in different portions of the stomach and by exerting pressure through the appropriate abdominal muscle groups, he can bring up the one desired. Finally, he swallows a pint of water and a half pint of kerosene, then stands about 6 feet from a candle burning in a brass box open at the front. The kerosene being of lower specific gravity is brought up first, in small jets which dramatically burst into flame as they approach the candle. When the kerosene is exhausted the water spraying from his mouth apparently quenches the flames.

Rumination in infants and imbeciles is quite as common as it is rare in adults. It may be related to the "cage sicknesses" of childhood, such as head banging and nail biting. Others describe it as merely an occupation to while away the time.[10] The chief argument for this latter view is that infants never ruminate when they are being amused or when they know they are being watched. In some children rumination becomes a serious feeding problem, for they spit out the returning food and lose weight as a result. This habit can be overcome in a very short time by the use of a Siegert balloon sound, which acts as an effective cork for the cardia after meals.[11]

Many writers have stressed the hereditary aspect in the tendency to rumination, but in this series only the actor had any history of the sort, and in this instance it had skipped the parental generation. Both Mueller[6] and Runge[12] have reported so-called "rumination families." Mueller described a father who died of scirrhous carcinoma in the constriction of an hour-glass stomach, who had ruminated for at least fifteen years and whose two sons were ruminants without the knowledge that their father was so afflicted. Runge recorded a grandfather, son and a grandson who were ruminants, each without the knowledge of the other. In both of these families it is evident that there was no conscious imitation and in the series here reported, I could find no instance in which the patient had seen another ruminant.

To gain a concept of the mechanism of rumination we must review our knowledge of the physiology of the upper digestive tract. Food delivered to the esophagus by the pharyngeal constrictors is propelled down its length by regular peristaltic motion under the control of the vagus nerve. Cannon[13] has shown that a bolus passing downward is held at the cardia until a second swallowing act is performed which constitutes the stimulus for the relaxation of the sphincter, allowing food to enter the stomach. Therefore, we should expect that just prior to rumination the patient should swallow. Toussaint[16] has observed it in the herbivora, and I can record this observation in man. The actor always goes through a

swallowing motion just before the gastric contents return. During gastric digestion, the cardia is in a state of tonic contraction, and in some individuals even very strong retching movements are insufficient to relax it; in others stimulation of certain portions of the mucous membrane of the mouth, swallowing, or even a disagreeable psychic influence will be sufficient for relaxation. Ruminants must obviously fall in this group.

There is one extremely interesting and important observation on the action of the cardia in the cat, which was made by Cannon in 1902.[14] He noted with the Roentgen ray a rhythmic regurgitation from the stomach into the esophagus. "The barium mixture runs up to the level of the heart and sometimes even into the neck and then back again. It takes place without any sign of reverse peristalsis and seems to be due to quick contraction of the lower esophagus." Unfortunately, no one has been able to reproduce the results in check-up experiments.

Since the advent of the Roentgen ray the pathologic anatomy of these patients has been more often noted. Autopsies had been hard to obtain, infrequent and inconclusive. Riesman's case showed nothing abnormal. Berg[15] reported a complete spindle-shaped dilatation of the esophagus. The father in Mueller's family showed an hour-glass stomach with a carcinoma at the site of the constriction and an esophagus dilated to the diameter of the small intestine. From the few reported autopsies, we can assume nothing definite.

It is important to note that in the majority of human routine Roentgen ray studies the stomach was found to be normal in size, shape and motility. In contrast to this, the stomach of ruminant animals is divided into four anatomic chambers of which the first two are merely receptacles for food, which will be rechewed when the animal finds the leisure to do so. To carry the comparison a step further, we find that the mechanism is also different with them. Toussaint[16] made an exhaustive study of the pressure changes in the thorax, trachea, upper respiratory tract, and rumen of the cow in the act of rumination. Even fifty years later one must pause to pay sincere homage to his skill, technical cleverness and untiring patience. By a series of superimposed simultaneous, kymographic records of the pressure variations in all the above areas he proved beyond argument that—

1. As rumination commences the diaphragm descends and is fixed. The glottis is closed and the ribs rise, all tending to lower the intrathoracic pressure to a very appreciable degree.

2. The rumen (proximal gastric pouch) is passive during the entire act.

3. The returning bolus must be quite fluid and is aspirated out of the inert stomach by the influence of the suddenly lowered intrathoracic pressure.

The conclusions I will draw regarding the mechanism of human

rumination are based on fluoroscopic observation of two of this series while they were ruminating. This was done through the courtesy of Dr. Henry Pancoast of the Hospital of the University of Pennsylvania and his associate, Dr. Karl Kornblum.

It will be recalled that Dr. T. R. C. had a predilection for eating marshmallow desserts twice, and this was a help in the preparation of the barium mixture. We used the ordinary amount of barium in a water suspension flavored with marshmallow whip. Our first attempt was a failure, because the mixture settled to the bottom of the fasting stomach and promptly disappeared through the artificial stoma. Two weeks later the technique was changed and he was given the same mixture an hour after a heavy breakfast. This time he ruminated well. We only saw the barium in the esophagus once, half way up and so no conclusion can be reached from this, but in the recumbent posture we were able to note significant changes in the stomach. It seemed that most of the food was held in the upper pole of the stomach, giving the effect of an inverted pear. Whenever rumination occurred there was a general contraction of a squeezing type, which relaxed when the act was over. In each instance, the mixture ascended the esophagus so fast we could not see it, but there was no doubt in our minds that the upper portion of the stomach was contracting like a bulb and squirting part of its contents into the esophagus.

For the actor no extra preparation was necessary except that a huge amount of the barium mixture had to be used. He drank it out of a pitcher and as the stomach became more and more filled we were surprised to see a large amount of the mixture course through the pylorus into the small intestine. From this it was evident that during his act he must use both the stomach and intestines as a reservoir. Several films were made with the stomach and intestines full. He was then asked to empty his stomach and we saw him hold his breath, then the barium shot into the esophagus and out the mouth in a steady stream. The stomach seemed to be emptying itself in the manner of a distended balloon diminishing in all dimensions equally, thus delivering the barium mixture to the lower end of the esophagus which contracted and relaxed rhythmically. No peristalsis nor reverse peristalsis was noted. This action continued until the stomach was almost empty when he was asked to stop. The roentgenologist was then able to push some of the barium from the intestine back into the stomach and the patient brought this up when asked to. A second attempt to do this was unsuccessful. The behavior of the stomach here is probably a mean of two factors. There is every reason to believe that contraction of the abdominal wall must have played a part in helping a stomach stretched to such dimensions to empty itself. However, when a major portion of the barium was ejected the diminution in size of the stomach continued and it is probable, therefore, that the gastric

musculature was doing its part also. This idea is strengthened because he was able to regurgitate the small amount of fluid which Dr. Kornblum pushed from the duodenum into the stomach.

We may make the following conclusions from these Roentgen ray observations:

1. Pressure changes in the thorax seemed to play no part.
2. During rumination the stomach empties itself by a diminution in size in all diameters, which is probably an expression of both the tightening of the abdominal muscles and the squeezing contraction of the gastric musculature.
3. The bolus is delivered to the mouth by rhythmic strong contractions of the lower portion of the esophagus, which are squeezing in type.
4. No evidence of organic or functional hour-glass stomach or cascade stomach was noted.

Except for two of Kohlmann's cases and the results here shown, adult rumination had not been seen fluoroscopically, mainly because the barium mixture is so unpalatable that the patients will not regurgitate. To overcome this, Kohlmann devised a "barium beef steak" which gave both bulk and flavor to the meal and was well ruminated. He concluded that the stomach seems to take an active part in rumination, dividing itself by a band of contracting muscle into a functional hour-glass form, from the upper portion of which food is shot into the esophagus. We did not observe any hour-glass deformity, but we feel that the human stomach seems to assume more than a passive rôle in the act of rumination. This is in strong contrast to the herbivorous animals whose food seems to be aspirated out of the inert rumen by lowered intrathoracic pressure. Mueller's reported hour-glass stomach, the site of a carcinoma, therefore assumes a new importance. It stresses rumination in connection with an organic hour-glass stomach, and for Kohlmann it raised the speculative question whether the long-standing irritation of a functional hour-glass constriction gave rise to the carcinoma. It shows also that a serious or fatal lesion may supervene in the stomach of a patient already a ruminant and puts us on our guard to inquire thoroughly into the length of time the rumination has been going on.

Allied to rumination is the "nauseless" vomiting seen in certain adults. These individuals can vomit at will without effort or discomfort, but they bring up the entire gastric contents at once. I have an obese female patient, aged fifty-five years, who has been able to do this since she was fifteen, and now uses the faculty as a convenient safety-valve when the gall bladder disease from which she suffers causes upward epigastric pressure.

Practically every observer has been impressed with a neurotic tendency in merycoles. All the men here recorded are fidgety and neurasthenic. The actor once became so excited that he could not

go on with his act and the patient with the persistent achlorhydria is certain at every visit that he is afflicted with various fatal maladies. The stories elicited from ruminants have almost a Münchhausen tinge. They all say the food tastes good, often better than when first eaten; in fact, one reported patient could only enjoy the proper taste of food during rumination. M. J. K. has put his faculty to a useful purpose. For several years he has been kept on a lacto-vegetarian diet for cardiorenal disease. Nevertheless, he indulges his fondness for meat quite often, spitting it out on second arrival in the mouth. As in the case of our physician, some can exercise a selective action and bring back only sweets or solids or highly-seasoned food.

Most ruminants find their faculty very embarrassing and do everything possible to hide it from general observation. Therefore, it is extremely rare to find a man who is eager to give publicity to the voluntary control of his stomach. H. A., the actor, is the first merycole to be recorded in the American literature who earns his living by gastric gymnastics. The only other case of this sort in the general literature was reported from Munich in 1913. He was an actor in a fair at that city and swallowed a large amount of water in which were several live gold-fish and a frog. He would then bring back either gold-fish or frog as the audience desired. The selection was not made in the stomach but in the mouth. If the frog came up first and was not desired it was quickly reswallowed. This man was observed fluoroscopically by Dr. Gulat-Wellenberg, who watched a frog injected with barium descend into his stomach and return again into the mouth. The observation was reported as a medical curiosity and no attempt was made to explain the mechanism.

It may be objected that our actor is an instance of voluntary vomiting, such as was cited earlier; but a review of his history proves him to be a ruminant who has developed his faculty to this astounding degree. The unusual behavior of his stomach he first noted as a boy, when after swimming, the water he had swallowed returned to his mouth at regular short periods. He became notorious among his playmates for this trick and learned to swallow larger amounts of water for their amusment. He states that he was once thrown out of a street café for ordering and drinking an inordinate amount of water. He then came to the attention of an Italian show owner who played him in Italy in a side show and taught him the rudiments of all the tricks which he now exhibits. He is a hearty eater and is especially hungry at the conclusion of each performance, but only remembers involuntarily ruminating solid food in three instances. The interest he provoked among Continental physicians led him to inquire into his family history. Neither of his parents ruminated, but his paternal grandfather whom he never saw was said to have done so for many years. He never saw any individual who could

ruminate. Clinically he is quite unusual in that he has complete voluntary gastric control and can regurgitate either a large or small amount of gastric contents, no matter what their nature.

(As a conclusion to the presentation of this paper, a motion picture of Hadji Ali's performance was shown.)

Summary. 1. A series of six human ruminants are described, five of whom were met in clinical practice, the sixth being an actor who permitted studies to be made upon himself.

2. The clinical findings in this syndrome are described.

3. Two of these individuals were observed fluoroscopically while ruminating.

4. The mechanism involved in the act of rumination is suggested.

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A STUDY OF STOOLS CULTURED FOR ENDAMEBA HISTOLYTICA FOR DIAGNOSTIC AND OTHER PURPOSES.

By Carlo J. Tripoli, B.S., Ph.G., M.D.,
INTERN, CHARITY HOSPITAL, NEW ORLEANS, LA.

(From the Laboratories of Clinical Medicine, School of Medicine, Tulane University of Louisiana.)

During the last half-century many attempts have been made to cultivate Endameba histolytica and other entozoic amebas in artificial media: but though numerous claims to success have from time to time been made, it is only recently that any methods have been devised which are at once sufficiently authenticated to be credible and sufficiently straight-forward to admit of ready confirmation by workers other than the original claimants. Most, if

not all, of the earlier "successes" are now know to have rested upon a misidentification of the organisms cultivated or to have involved familiar fallacies of observation or interpretation, and as none of them has yet been substantiated, or has been able to bear critical later examination, it now seems unnecessary to review the history of this subject anew.

Apart from certain debatable results announced by Cutler,[1] the first manifestly successful attempt to cultivate any entozoic amebas *in vitro* appears to be that of Barrett and Smith,[2] who cultivated two intestinal species of endameba from cold-blooded vertebrates—E. barretti from turtles and E. ranarum from frogs. Their cultures of the first species were independently examined by Taliaferro and Holmes,[3] with entirely confirmatory results; while a full account of the cultivation of E. ranarum has also been published by Barrett and Smith[4] and verified by Taliaferro and Fisher.[5] While the method devised by Barrett and Smith appears to be adequate for the species which they studied, it does not seem to be adaptable to the cultivation of all entozoic amebas.

In 1924, Boeck and Drbohlav[7] announced that they had succeeded in cultivating Endameba histolytica by an entirely different method, and since the publication of their early papers many independent workers have been able to confirm their results.

Under the direction of Dr. F. M. Johns, Director of the Laboratories of Clinical Medicine in Tulane University, I have cultivated one strain of pathogenic ameba, E. histolytica, through 86 subcultures since June, 1928, many different strains of E. histolytica were initiated and studied in culture, and numerous attempts were made to perpetuate cultures of other nonpathogenic amebas obtained from the routine microscopic and cultural examination of a large number of specimens of feces.

Composition and Preparation of Culture Media. In obtaining and maintaining a large number of cultures of E. histolytica many details of producing a uniformly successful medium have been studied. We have tried all of the probable variants based on the original medium of Boeck and Drbohlav. Although this medium is apparently suitable for cultivation and propagation of amebas, it did not give uniformly successful results for routine cultures of stools for the purpose of diagnosing the presence or absence of pathogenic amebas. Dobell and Laidlaw's[6] modification of Boeck and Drbohlav's[7] original media for the isolation and cultivation of amebas was found to be apparently more suited to routine use. This medium furnishes a definite source of assimilable carbohydrate as food for the amebas, and further provides a mild bacteriostatic agent (acriflavine) which may be used to inhibit the growth of such frequently found bacterial flora as would preclude the obtaining of an initial positive culture. In our work we have sought to develop this modification in order that it could be used in the average labora-

tory for routine diagnostic purposes. The following method, in detail, of preparing this modification of Drbohlav's media has seemed to give uniform results:

I. Ingredients of Media.[8] (*a*) *Serum-Ringer Solution.* Beef or human blood is obtained. After clotting it is placed for twenty-four hours in a refrigerator. The clear serum is pipetted off and mixed with Ringer's solution in the proportion of one part of serum to eight parts of Ringer's solution. Sterilization is accomplished by passing the fluid through the *large* type Seitz-Wertz filter, which permits the fluid to pass only through the filter pad. Filtration is accomplished by use of full vacuum. The filtered, sterile, diluted serum is immediately pipetted off with a 50-cc. sterile pipette and placed in sterile flasks 50 cc. to each flask. These flasks are kept at 8 to 10° C. until ready for use. Inactivation of the mixture (56° C. for thirty minutes) is not necessary.

(*b*) *Starch.* Rice starch possesses the necessary uniformly small grains which are readily ingested by the amebas, and further is not easily hydrolyzed when suspended in fluid. The method of sterilizing the starch without charring or disintegrating and rendering it soluble has presented quite a problem. Dobell and Laidlaw state that, "After various trials we have found, contrary to the indications in some works which we have consulted, that solid rice starch can be completely sterilized without being charred, disintegrated or rendered soluble, by subjecting it to a temperature of 180° C (dry heat) for one hour. It should be dry before heating and heated in small quantities, not in bulk." An attempt was made to carry out these instructions in every detail. By the method outlined above, we found that rice starch was charred slightly and rendered more soluble. It was found that even as low a temperature as 130° C. (dry heat) for thirty minutes would char and render the starch soluble; which enables it to be readily utilized by the starch splitting bacteria in the cultures. As a result the media became highly acid in a short time and the amebas inoculated grew poorly and often were overcome by bacterial growth.

The following method of sterilization was developed which apparently fulfills the requirements and has given entire satisfaction:

The starch is weighed out in 0.2 gm. quantities, placed in small soft filter paper tubes which are made by rolling a 3½ by 5 cm. piece of thin filter paper about a pencil and in which the starch is kept in place by lightly crimping the ends of the paper tube. The filled tubes are placed in test tubes which are then plugged with cotton and covered with several layers of wrapping paper which is well tied down over the end of the tube, and the whole assembly autoclaved at 15 pounds pressure for fifteen minutes. After autoclaving, the paper covering is removed and the tubes are placed in a hot air oven or incubator to evaporate the little moisture that may have condensed upon the walls of the tube.

(*c*) *Acriflavin Solution.* A 1 per cent solution of acriflavin is prepared and sterilized in the Arnold sterilizer. Acriflavin solution keeps fairly well when protected from light and at a low temperature.

(*d*) *Egg Base.* Four eggs are emulsified with 50 cc. of normal saline and poured into 1½ by 15 cm. tubes to a depth of approximately 2 cm. The tubes are placed upright in the water bath and heated to 80° C. for sufficient time to coagulate to a firm consistency, after which they are autoclaved at 15-pounds pressure for fifteen minutes in the upright position. Amebas grow best upon a flat surface.

II. Assembly of Media. (*a*) The starch is added (0.2 gm.) to the serum-Ringer solution (50 cc.) by placing the small paper tubes into the flask. Slight agitation opens up the paper and liberates the starch.

(*b*) Acriflavine is added by transferring 0.1 cc. of the 1 per cent solution to 50 cc. serum-Ringer starch, which gives an ultimate dilution of 1 to 50,000. Some samples of acriflavin require a greater concentration (1 to 25,000) to retard the growth of unfavorable flora.

(*c*) Four to 5 cc. of sterile serum-Ringer's solution plus the starch and acriflavin are then poured into the tubes containing the coagulated egg. The tubed culture media should be stored in the refrigerator until used. At the time of inoculation the media should be warmed to 37° C. An equal number of tubes should be prepared, omitting the acriflavin.

The pH of the prepared media varies from 7.2 to 7.8 and needs no adjustment, this being the optimum range of hydrogen-ion concentration determined for E. histolytica.

Drbohlav advocates the addition of 5 gm. per liter of potassium acid phosphate to the media which is adjusted to a pH of 7.4. This, we have found, to be unnecessary as the medium is capable of adjusting itself to the original pH even after forty-eight hours of bacterial growth which tend to form organic acids. We have found, as Dobell and Laidlaw, that alkalies as well as acids are injurious to growth of endameba in direct proportion to their concentration.

Method of Inoculating, Examining and Transplanting Cultures. A particle of fecal material about 1 or 2 mm. in diameter is picked up on a wooden applicator and is transferred to a tube of plain, and a tube of acriflavine charged media which have been warmed to about body temperature.

With soft or dysenteric stools, which are more apt to contain vegetative amebas, the material used for inoculation should be obtained fresh from the patient. Proctoscopic removals and rectal washings should, similarly, be inoculated immediately.

With formed or hard stools, which are more apt to contain cysts, the cold stool will suffice even though it be several days old. We have obtained the same results with cysts fresh from the patients or with those kept in the refrigerator for several days.

The tubes are incubated in an upright position at 37° C.

Maximum growth is usually seen on the third or fourth day of incubation. On the fifth or sixth day the amebas usually die unless they are transplanted into fresh media. Under cultural conditions very few amebas encyst, but with frequent transplantation they can be propagated in the vegetative form for an unlimited period.

Examination of the cultures is made by skimming the débris of starch and bacteria from the surface of the coagulated egg with a capillary pipette having a large lumen (1 mm.) which has been scratched and broken to present a square tip. Use a Wright's rubber bulb to produce suction. A fraction of a drop of material is removed, placed on a slide, cover glass added, and examination made with the 16-mm. objective.

To transplant the culture a drop of the material is transferred to fresh media that has been previously warmed.

Differentiation of Pathogenic and Nonpathogenic Amebas Cultured.[9] There is no remarkable change in structural detail or behavior of the amebas in their cultural environment, the main features conforming closely to the accepted descriptions. In culture, however, the unlimited number of amebas available for study permits of greater emphasis being placed on minor individual peculiarities. The nuclear structures as shown by appropriate stains retain the same characteristics exhibited by amebas obtained from their natural habitat.

I. Endameba histolytica. Cultivation of this ameba produces a reduction in size, a slowing of activity and a diminution in the clear, glasslike appearance of the ectoplasm which characterizes the organism in stools. In the feces, it is unusual to find bacteria within the cytoplasm, as we often do in culture. The nucleus, usually invisible in the living specimens from feces, is defined with ease in wet preparations from culture. In a way, the general effect is to cause the organisms to resemble more closely some strains of Endameba coli as found in liquid feces.

At room temperature the amebas when first removed from the culture are found to be rounded and motionless, but movement begins after an interval of several minutes. This movement is highly characteristic. It is comparatively swift, progressing at about 30 microns per minute. It is fairly definite in direction; it is as if one had the impression that the ameba has a purpose in moving and that it is not to be delayed en route.

The shape of the ameba in movement is also important. Viewed with the low power of the microscope, the appearance of a large number of quadrilateral objects in motion is highly characteristic. Viewed with the oil-immersion lens the margin of the ameba is seen to be smooth with the clear ectoplasm more or less well differentiated from the endoplasm. With careful attention to light and focusing, the nucleus can be identified by the appearance of a refractile ring

of granules, like a string of beads. The karyosome cannot usually be defined; if defined, it is seen to be a tiny dot, usually central in position. The appearance of the karyosome, or rather, the lack of its appearance, is a most important factor in the identification, as in E. coli the karyosome may be seen as a large eccentrically placed granule with a nuclear ring composed of large highly refractile granules.

The small races of E. histolytica are essentially similar to the larger strains. On account of size, one may confuse them with E. nana, I. williamsi, or D. fragilis. However, by a careful study of the movements and structure, one should easily be able to make a diagnosis. It may be necessary to stain these smaller amebas before reaching a conclusion as to identity. Subcultures of E. histolytica tend to show more characteristic forms, while the non-pathogenic amebas will hardly grow at all, and are soon lost on this particular media.

Encystment of E. histolytica in culture is of too infrequent occurrence to be of value in diagnosis. Cysts were produced irregularly, some strains producing numerous cysts on the third or fourth day, while with other strains cysts were seldom or never found. The cysts in culture were identical with those observed in feces—the glycogen content being particularly high. Culture-produced cysts were capable of initiating fresh cultures after being kept for thirteen days at 8° C.

II. Endameba coli. This ameba has a tendency to succumb in culture; that is, in the medium prepared as described most strains did not survive the first transplant. I have come to regard this as a point of some value in differential diagnosis, as E. histolytica is usually easily maintained in culture.

The majority of the strains observed lacked the characteristic motion of E. histolytica. At room temperature (70° F.) there is little tendency toward progressive movement; they prefer to merely change shape, lolling about in practically the same position. The outline of the ameba is rarely quadrilateral as is characteristic of E. histolytica but is inclined to be irregularly circular. There may or may not be a sharp differentiation between endoplasm and ectoplasm; when closely compared, there is little difference from that observed in E. histolytica. The marginal outline is smooth. Visibility of the nucleus is good as a rule. When visible, the presence of a large eccentrically placed karyosome is the concluding feature of the diagnosis. They are more prone to ingest bacteria, while E. histolytica are usually satisfied to gorge themselves with starch granules.

III. Iodameba Williamsi. The size, characteristic movement, marginal outline, and the visibility of the nucleus of this ameba are sufficient to permit diagnosis from a study of the living cell. It is considerably smaller than E. histolytica, so much so that a search

with very high magnification is necessary to determine their presence in a culture. The movement is very slowly progressive, indefinite in direction and somewhat listless in execution. The marginal outline of the well differentiated ectoplasm in some stage of the movement is found to possess coarse serrations, a characteristic not observed in other amebas included in this work. The karyosome is practically always visible as a large highly refractile object resting in a clear area. With care in distinguishing these points, there should be little confusion with Endameba nana, with which it is most likely to be confused.

IV. Endameba nana. All strains obtained in culture were small, measuring about 9 microns in diameter. The character of the movement and form in movement very closely resemble small races of E. histolytica. The pseudopodia are well differentiated and consist of ectosarc. The marginal outline is smooth. Progressive movement is fairly rapid. However, the large karyosome of E. nana is usually plainly visible as a large highly refractile inclusion. The presence of the latter feature in an ameba resembling small races of E. histolytica should be sufficient to make a diagnosis.

The Influence of the Bacterial Flora upon the Initial and Subsequent Growth of Amebas in Culture.[6] "Pure cultures" of amebas, such as can be obtained by the Boeck-Drbohlav technique and its various modifications, are "pure" in the sense that they contain one species of ameba alone; but they inevitably consist of amebas accompanied by a diversity of bacteria (and possibly other microorganisms). E. histolytica, and all other species studied, largely depend in cultures upon these associated organisms for their food supply and it does not seem feasible to eliminate them entirely.

Strains of amebas initiated from free forms in feces are always accompanied by a great many different bacteria derived from the intestinal contents. For the cultivation of many of these bacteria the various media employed are often excellently suited; and consequently they are propagated, along with the amebas, whenever subcultures are made, but it always happens that the bacterial flora originally present in initial cultures undergoes considerable changes as regards the species and their relative proportions on continued cultivation. For a variable number of generations the flora fluctuates, finally reaching a state of stable equilibrium by a process of natural selection. In this process the amebas may sometimes be exterminated, and for this reason freshly isolated strains of amebas may require careful watching for some time before they begin to grow with regularity. During this period in the presence of rapidly-growing unfavorable bacteria frequent transplants to fresh media is the most important consideration. Growth under constant conditions of media and temperature can be foretold with certainty.

Obtaining of primary cultures of amebas by methods involving such a number of unknown variables, which sort themselves out, in the end by chance, is obviously unscientific. Success often depends largely upon luck. It is therefore clearly desirable to discover some means of controlling the composition of the entire bacterial flora at will; but this has been found to be extremely difficult.

That the bacteria in a culture of amebas exercise a profound influence upon its welfare, no one who has attempted to cultivate these protozoa can doubt. It is only necessary to have acid-forming bacteria present to convince the most skeptical. Such organisms, by acidifying the medium to a degree which the amebas cannot tolerate, may wipe out a flourishing culture in a few hours. For example, starch-splitting bacteria, if introduced into cultures containing this carbohydrate, soon make further cultivation of the amebas impossible; but if they are exterminated by passage through acriflavin-containing media the culture may be carried on indefinitely.

Immunologic Reactions Possible with Cultured Amebas and Extracts of These. Recently C. F. Craig[10] has stated that he has found that immune substances are produced of which he can obtain evidence by serologic reactions. The development of a complement-fixation test, which would be specific, would indeed be welcome. Especially in some cases of suspected liver abscess where a diagnosis, at present, can hardly be made except by surgical intervention.

We have endeavored to investigate the problem from the viewpoint of allergic skin reactions using glycerin extracts of luxuriant cultures of Endameba histolytica. Glycerin in strength of 90 per cent was used to extract the organisms. Cultures were centrifugalized at low speed for about fifteen to twenty seconds. The sediment upon examination showed that there was approximately an equal volume of E. histolytica with the bacteria and starch. This sediment was then mixed with an equal volume of 90 per cent glycerin. The mixture was allowed to remain in the incubator for three days, followed by careful centrifugalization at high speed. The supernatant fluid was carefully pipetted off and tested for sterility by inoculating bouillon tubes. The sterile extract was injected intracutaneously (0.2 cc.) into a number of patients known to have amebic infection, and an equal number of controls in whom no evidence of infection could be found. In all of those patients known to have the infection, the skin test was positive. A positive reaction consisted of a small bleb about 2 mm. in diameter surrounded by a red areola about 1 cm. in diameter. In those patients in whom by ordinary laboratory methods E. histolytica could not be demonstrated, reactions were seen varying in intensity from a completely negative one to a reaction similar to those obtained in the infected patients. We have sought an explanation for this, and it seems

plausible that besides extracting the antigenic properties of E. histolytica, such a crude extract must contain peptone or other split protein products which would occasionally give a nonspecific reaction. The use of alcohol as a menstruum as recommended by F. C. Craig seems to eliminate the factors giving nonspecific reactions. He states that alcohol extracts the antigenic principles of E. histolytica, but does not extract those organisms which produce the nonspecific reaction; namely, certain strains of streptococcus. We have not employed alcoholic extracts as yet; however, it seems to be of quite a distinct value and an effort will be made to confirm Dr. Craig's observation using such antigens in cutaneous tests.

Diagnostic and Differential Diagnostic Aids Made Possible by Culturing Feces for Amebas. In the discussion of the composition and preparation of the culture media, mention was made of the practical application of the method in the clinical laboratory. In the examination of stools for the presence of the various forms of E. histolytica, one cannot always make a certain diagnosis. Cysts are sometimes encountered which are atypical or the *number* present may be extremely small, and a diagnosis by the ordinary routine methods is most difficult even with the employment of appropriate stains. Properly-stained wet-fixed smears are superior to the ordinary intravital staining with iodin we admit, but this requires not only considerable technical ability to stain, but much valuable time in finding amebas after staining, as well. Therefore, a method which may be employed in the ordinary clinical laboratory and one which does not require a great deal of time would be of quite an advantage. With the cultural method both atypical cysts and immobile vegetative forms may be propagated and their characteristics studied in culture. In this way careful and detailed study is possible and a positive diagnosis can be made in nearly all instances.

One can readily see that in the case where only a very few of the organisms are present microscopic examination of the fresh specimen may not reveal them, here the cultural method should prove of considerable aid, in that although only one or two organisms may be originally introduced, examination of the culture at the end of forty-eight to seventy-two hours reveals large numbers of vegetative forms which are characteristic of the species. Therefore, we conclude that the introduction of the cultural method as an aid to the ordinary diagnostic methods will eventually prove to be quite an advance in diagnostic laboratory technique.

Comparative Diagnostic Results Obtained by Means of Cultures and the Direct Microscopic Examination. During the past six months, routine stool examination employing both the microscopic and the cultural methods has revealed quite interesting results. During the course of this examination nearly 300 specimens have been carefully considered. A microscopic examination employing

the method advocated by F. M. Johns[11] for the concentration of cysts was made. In the case of diarrheal stools direct microscopic examination was made of various parts of the stool for vegetative forms. A record of the microscopic examination was made and a particle of stool inoculated as outlined above into suitable culture media. After forty-eight hours and again after seventy-two hours the culture was examined for amebas. In cases of E. histolytica infection, practically 100 per cent of those which were found to contain amebas by direct microscopic examination also gave a positive growth on culture. On only one occasion has microscopic examination given negative results, and cultivation revealed a positive result. In this case, a liquid specimen from a patient with acute diarrhea was obtained about 10.00 A.M. On two different occasions during the day the specimen was examined by two competent observers with negative results. Examination of the cultures two days later revealed a luxuriant growth of amebas which were characteristic of the species E. histolytica.

The Incidence of Amebic Infection in Louisiana as Shown by a Combined Cultural and Microscopic Study of 258 Patients. In a recent review of the literature, we have not been able to find any record of the incidence of amebic infection in Louisiana. C. F. Craig[12] states, "It is now quite generally accepted that incidence of about 10 per cent of infection with E. histoloytica may be expected in carefully-conducted surveys of the population of most localities in the United States; with a *higher* incidence of infection in institutions and in regions along the Mexican border and the Gulf Coast." A routine examination was made of the feces of 50 patients visiting the Outpatient Department of Charity Hospital during the summer of 1928. Specimens were taken regardless of the complaint and in the order in which they presented themselves for medical advice. The remainder of the patients, 258 in number, were selected from the clientele of F. M. Johns and from the students of the present junior class in the Tulane School of Medicine. Six of the patients from Charity Hospital were carriers of the encysted form of E. histolytica. Five of the patients seen by F. M. Johns were carriers of cysts and 2 of them who were complaining of severe diarrhea with tenesmus had vegetative forms of E. histolytica in the stool. Of the 108 junior medical students examined 4 had encysted E. histolytica in their stools. Thus we have an incidence of 6.97 per cent of amebic infection, either with cysts or vegetative forms, in this somewhat selected group of Louisianians. From this survey we may, in a general way, estimate the incidence of E. histolytica infection in Louisiana. Here we have a series of patients from the lower strata of society from Charity Hospital and those from the higher walks of life and a number of apparently healthy students in the present junior medical class. From these studies

one may conclude, with some conservatism, that the incidence of amebic infection in Louisiana among the general poulation is probably somewhat below 7 per cent.

The Importance of a Cultural Method of Examination in the Detection of "Carriers" From a Public Health Standpoint. The prevalence of the infection of E. histolytica has been estimated at approximately 10 per cent in various parts of the United States. Here, in Louisiana, we have found that approximately 7 per cent of the people examined show either cysts or vegetative forms in their stools. In various institutions the incidence may be very much greater, due to the fact that if one of the kitchen force should be a "carrier" that everyone in the institution may take in cysts of E. histolytica with their food and subsequently become infected. That the infection is disseminated among the population by carriers of E. histolytica is little in doubt.

To determine which are the "carriers" in a community, examination should be made of the stools of all the individuals at approximately the same time. That examination of all the individuals should be done at the same time, should be stressed. If the stools of only a few individuals are examined every day or so and the treatment given these cases, the eradication or even a great reduction in the incidence cannot be hoped for. It is now generally accepted that there is no immunity developed after infection with E. histolytica. By the time the survey is complete it is very probable that those first examined are reinfected by those who are last to be examined; especially if the individuals come in contact with food and drink of others.

The task of general stool surveys at first seems quite formidable. The examination of fresh stools for cysts requires the services of a protozoölogist or a technician especially trained along these lines. This is quite an added expense to any laboratory.

With the advent of the cultural method as a diagnostic aid, the examination "*en masse*" may be conducted at the expenditure of only a minimum of time and effort on the part of the health department laboratory.

The method of inoculating, examining and transplanting the cultures has been described and its simplicity of practical application is obvious. The cultural method may be used by the average technician in the laboratory. The diagnosis of the amebas in culture is quite easy.

The problem of diagnosis of carriers of amebic infection is most important for at present we have a specific therapy which is quite efficacious. The cost is moderate and the treatment is not trying on the patient. The rewards, from a public health standpoint, would repay, by many fold, the effort, time and money expended The efficiency and productiveness of a community is directly proportional to the health of the individuals comprising its population.

Summary and Conclusions. 1. The influence of the bacterial flora upon the initial and subsequent growth of amebas in culture is very important, yet it does not seem feasible to eliminate the accompanying bacteria entirely.

2. The factors producing death of the amebas in culture are multiple, each playing its own particular rôle.

3. The immunologic reactions possible with cultured amebas and extracts of these give promise as a valuable aid in diagnosis.

4. The cultural method here described of stool examination for diagnosis of presence of E. histolytica has so far been equal to any laboratory means of diagnosis, and may eventually prove superior to the direct microscopic method.

5. From a study of 258 private and dispensary patients and medical students, it is estimated that the incidence of amebic infection in Louisiana is a little below 7 per cent.

6. Use of the cultural method of stool examination for E. histolytica would result in considerable saving of time and personnel in public health work in the detection of carriers of E. histolytica.

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INFECTIONS PROBABLY DUE TO MORGAN'S BACILLUS.

By Rigney d'Aunoy, M.D.,
DIRECTOR OF LABORATORIES, CHARITY HOSPITAL, NEW ORLEANS, LA.

(From the Pathological Department, Charity Hospital of Louisiana, New Orleans, Louisiana.)

Since its first description, in 1906,[1] the pathogenicity of Morgan's bacillus has been much debated. Although Morgan described the organism as a pathogen concerned in the causation of diarrheal conditions, especially in children, his conclusions have never been generally nor entirely accepted, even though his studies were later confirmed by himself and Ledingham,[2] Ohrum and Bahr,[3] and Bahr and Thomson.[4] Subsequent observations have shown Morgan's bacillus to be rather widely distributed, isolations having been made by Kligler[5] and Fridtjof Bang[6] among others, from the soil, roaches, and mice as well as from the feces of healthy and sick individuals. In spite of this, there is increasing evidence that the organism can under certain conditions invade and initiate disease processes in man.

Tribondeau and Fichet[8] and later d'Herelle[9] found Morgan's bacillus in the stools of patients suffering from dysentery. Thjötta[10,11] reports its isolation in ulcerative colitis and fatal cholecystitis. Olaf Bang[7] isolated it from the feces of a patient with intestinal hemorrhage occurring during the course of purpura abdominalis. Magath and Jackson[12] isolated it in a fatal case of septicemia, with pyemia. Riding[13] describes it as a cause of pyelitis. Havens and Ridgway[14] discuss its occurrence as an etiologic factor in 13 cases of pyrexia, all presenting undoubtedly distinct and well recognizable clinical pictures.

It is the desire to here briefly review certain observations that have been made upon various biologic characteristics of Morgan's bacillus and to report its isolation from three human cases, believing that the exact status of the organism as a pathogen will be definitely established only by correlation of the information gained by such reports.

Morphologic and Cultural Reactions. Morgan's bacillus is a slender, slightly motile, Gram-negative rod averaging 1 to 3 μ in length when observed in young bouillon cultures. Large and bizarre involution forms are not uncommon, occurring especially in older cultures grown on agar. The hydrogen-ion concentration range of growth in peptone water for ten isolations studied was pH 4 to pH. 9 S and R colonies were differentiated. All isolations studied produced indol in peptone water, the more recent isolations giving especially strong reactions. Extensive fermentation studies gave regular acid formation with gas production in

glucose, levulose, and galactose peptone water. Browning was noted with acetate agar and no growth in citrate media. Gelatin was not liquefied.

Pathogenicity. Investigators agree that Morgan's bacillus is usually nonpathogenic for small experimental animals. Second generation cultures from Case III hereinafter reported were highly pathogenic for guinea pigs and white rats following intraperitoneal injection. This pathogenic power was not resident in cultures of the same isolation eight generations older and tested sixteen months later. Isolations from the other cases herein reported, as well as isolations made during the course of this study from the feces of two healthy children and from the feces of a case of typhoid fever were nonpathogenic for guinea pigs, white rats and mice.

Serologic Interrelationship. Immune serums produced in rabbits with the isolations from Cases I and III agglutinated only their homologous organisms. Serum from Case II weakly agglutinated organism from Case I and the Fly strain in dilutions of 1 to 10. Extensive absorption and agglutination experiments, to be reported in detail later, failed to show any serologic interrelationship between local isolations and other available strains. These results are in agreement generally with those of other investigators.

Case Reports. Case I.—L. D., white, female, aged twenty-three years, had malaise, headaches, loss of appetite, for three days before noticing temperature of 104° F. The blood count on the fourth day was 4750 white cells, with 72 per cent neutrophils. Blood culture on the fifth day was positive for Morgan's bacillus. The blood count on the sixth day was 9900 white cells, with 76 per cent neutrophils; on the twelfth day 9000 white cells with 76 per cent neutrophils. Agglutination tests with B. typhosus and B. paratyphosus A and B were negative on five occasions. There was slight diarrhea after the sixth day. Feces culture was negative for B. typhosus, B. paratyphosus and Morgan's bacillus on three attempts. Headache and myalgia were marked. There was fever for eighteen days, with marked morning remissions. Homologous isolation of Morgan's bacillus was agglutinated by the patient's serum in dilutions up to 1 to 240 on the tenth day of illness.

Case II.—A. L., female, aged three years, had had recurrent attacks of pyelitis accompanied by irregular fever for the past two years. The present attack was of four days' duration. The urine showed much pus, with a moderate trace of albumin. Morgan's bacillus was isolated from a catherized specimen of urine on two occasions. The homologous organism was agglutinated by the patient's serum in a dilution of 1 to 120. There was no agglutination with B. typhosus, B. paratyphosus A and B, but B. coli communis was agglutinated in a dilution of 1 to 10.

Case III.—A. M., white, female, aged three years, had had severe diarrhea for seven days and had lost some weight. The fever range was 100 to 102° F. There were five to eight profuse watery evacuations in twenty-four hours. Morgan's bacillus was isolated from stool. A homologous culture was agglutinated by the patient's serum in dilutions up to 1 to 200. There was no agglutination with B. typhosus, B. paratyphosus A and B, B. dysenteria, Shiga, Flexner, Hiss Y and Park.

Discussion and Summary. It is believed that consideration of the cases here reported points to the strong probability of Morgan's bacillus being concerned as an etiologic factor. Case I has numerous clinical features in common with those presented by the cases reported by Havens and Ridgway. The fever course, although somewhat shorter, generally approximates that of their cases. Headaches and myalgia were common features. No chill at the onset of illness was noted, however, a feature so common in their cases. Isolation of the organism from the circulation and its subsequent agglutination in high dilutions are naturally the most significant diagnostic criteria, and that especially in view of the constant lack of agglutination of other organisms by the patients' serum. Three months after recovery, agglutinins for Morgan's bacillus were not demonstrable.

In Case II, Morgan's bacillus was isolated from catheterized bladder urine on two occasions, and agglutinins were demonstrated in the patients serum for the homologous organism in rather high dilutions. In addition, the organism in Case I and that of another isolation were weakly agglutinated by the patient's serum. Another possible suggestive feature in this case was the rapid recovery and freedom from subsequent attacks over two years after administration of an autogenous Morgan-bacillus vaccine, even though previous attacks had neither been helped nor prevented by stock colon-staphylococcus vaccines.

In Case III, the organism was isolated from the stool and specific agglutinins were demonstrated for it. This feature causes the case to differ from those of Thjötta, who, though able to isolate Morgan's bacillus from the stools and from intestinal lesions at necropsy in cases of severe colitis, was never able to elicit agglutinins in the blood of his patients, not even in nonfatal cases.

The exact place Morgan's bacillus should occupy in the classification of microörganismal forms is still debatable. As Thjötta rightly points out, its inclusion in the genus Salmonella is probably not justifiable. It has far more points of biologic differences than similarity with the members of this group. In spite of its fermentation reaction it can undoubtedly be placed more appropriately with the Escherichiæ, with which it has so many common biologic characteristics. Its appellation as Bacillus metacoli (Morgani) as suggested by Dutch investigators is justifiable and possibly desirable.

Summary. The isolation of Morgan's bacillus in cases of pyrexia, pyelitis and colitis is reported. One strain isolated proved pathogenic for small laboratory animals. Agglutinins were demonstrated for homologous organisms in the blood of all three patients. Observations upon some biologic characteristics of the organism are presented together with a plea in support of Thjötta's position for noninclusion of the organism in the genus Salmonella.

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DIABETES INSIPIDUS AND LESIONS OF THE MID-BRAIN: REPORT OF A CASE DUE TO A METASTATIC TUMOR OF THE HYPOTHALAMUS.*

By T. B. Futcher, M.B.,

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

The etiology of diabetes insipidus still remains an unsettled problem. The two views chiefly advanced at the present time are first, that it is of pituitary origin and dependent upon a hypofunction of the posterior lobe, and second, that it is of nervous origin and due to lesions of the hypothalamus, particularly of the tuber cinereum or the corpora mammillaria. Although the pituitary conception has had most adherents since 1912, there have been those who have held to the view, based both on experimental and clinical grounds, that, although the posterior lobe of the pituitary may be involved in a tumor or cyst, the actual cause of the disturbance of water metabolism is located in the structures comprising the hypothalamus. The purpose of this paper is to review some of the evidence supporting these two views, and, to report a case of diabetes insipidus in which the pituitary was intact but in which there was a metastatic tumor involving the mid-brain, or hypothalamus secondary to a tumor of the lung.

Before presenting some of the evidence which has been advanced to support the pituitary conception of the etiology of diabetes insipidus, a brief statement concerning the embryology, histology and functions of the pituitary gland may not be out of place. The gland consists essentially of the anterior lobe, the posterior lobe and

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the pars intermedia, an epithelial envelope partially surrounding the posterior lobe.

The anterior lobe is developed from a diverticulum of the ectoderm of the primitive buccal cavity. It is essentially a glandular structure and its function has a very important bearing on growth and on the development of the primary and secondary sexual characteristics of the individual.

The posterior lobe is of nervous origin and is developed as a downgrowth from the floor of the embryonic brain. It is essentially made up of what have been considered neuroglia cells and fibers but it was known that columns of cells from the pars intermedia extended into it. Although it had been believed that it presented none of the features of a secretory gland, yet the work of Lewis and Lee[1] recently has shown that it actually contains groups of cells arranged even in the form of a tubuloracemose gland in infants up to four years of age. There is evidence, therefore, that it does contain cells which may perform a definite secretory function. It is important to note that Cushing[2] has demonstrated delicate nerve fibers of uncertain destination passing down the infundibular stalk and becoming lost in the upper portion of the posterior lobe. Previously, in 1911, Cajal had described nerve fibers passing into the neurohypophysis. In 1922, Hoenig reported nerve fibers in the neurohypophysis and stalk, as well as fibers passing through the infundibulum and apparently ending in the epithelial cells of the anterior lobe. These findings are reported by Fink[3] in his admirable review of diabetes insipidus.

Among the chief functions attributed to the extract of the posterior lobe of the pituitary gland are its pressor, oxytocic, respiratory, diuretic—antidiuretic, and melanophore expanding properties. To explain the latter it may be stated that hypophysectomized tadpoles become albinos, but when injected with pituitary extract they assume their normal pigmented color. In addition, the posterior extract influences carbohydrate metabolism acting through the hormone of the islands of Langerhans, and probably has some influence as a galactogogue.

The first evidence advanced to indicate that the extract of the posterior pituitary lobe influenced water metabolism was in 1906 when Schäfer and his associates Magnus and Hering showed that its injection into animals produced a transitory polyuria. Harvey Cushing, in 1910, in removing the posterior lobe of dogs, reported that this procedure was accompanied by transitory increase in the urinary flow.

Shortly after this there began to appear in the literature clinical evidences supporting the same view. The first clinical report was that of E. Frank[4] who, in 1912, reported a case of diabetes insipidus in a man who had been shot and in whom the Roentgen rays showed that the bullet had lodged in the sella turcica.

In 1913, M. Simmonds[5] reported a case of diabetes insipidus in a woman, aged thirty-seven years. Two months after an excision of the breast for carcinoma she developed a very marked polyuria. The autopsy showed, in addition to numerous other metastases, one involving and destroying the posterior lobe of the pituitary gland. This metastasis pressed on the pars intermedia of the posterior lobe but did not involve it or the anterior lobe. Simmonds believed that the polyuria was dependent upon the stimulating effect of the metastasis on the pars intermedia.

Harvey Cushing,[6] in his Shattuck Lecture in 1913, stated that his animal experiments and surgical experience in hypophysial disease strongly convinced him that there was a very intimate relationship between the polyuria of diabetes insipidus and pituitary lesions. Among his first 100 cases of pituitary disease the polyuria had been so marked that in 6 a diagnosis of diabetes insipidus had been made by the physicians referring the cases. He reported a remarkable case (which the writer saw personally) of polyuria in a woman aged forty and totally blind, who presented signs of hypopituitarism. This polyuria, which reached 12 liters daily and was accompanied by an insatiable thirst, followed a sellar decompression operation for relief of symptoms and lasted for a period of three months. Cushing believed that the polyuria resulted from an irritative lesion of the posterior lobe of the pituitary, sustained during the operation.

In 1913, also, important therapeutic evidence appeared which seemed to further substantiate the intimate relationship between the posterior lobe of the pituitary and the polyuria of diabetes insipidus. Von den Velden[7] and Farini[8] independently, found that extracts of the posterior lobe and pars intermedia caused a diminution of the polyuria in diabetes insipidus. Although von den Velden first demonstrated the efficiency of pituitrin, he failed to grasp its significance as a therapeutic agent, stating "there is little to favor the idea of substitution therapy." Farini, on the other hand, accepting the results at their true value, advanced the view that diabetes insipidus was a disease due to hypoactivity of the posterior lobe of the pituitary.

The observations of von den Velden and Farini were soon confirmed by many others and experience has shown that pituitrin, either given hypodermically or by nasal administration as a spray or by soaking pledgets of cotton with pituitrin and inserting them into the nasal cavity, as first advocated by Blumgart, has proven in many cases of diabetes insipidus to be most effective in checking the polyuria and consequent thirst, and is the most effective means we have at our disposal at the present time for relieving the distressing symptoms of the disease.

As has already been mentioned, Schäfer and his associates found that the effect of the injection of posterior-lobe extract was to pro-

duce a diuresis. The work of von den Velden and Farini and others later showed that, although diuresis is the primary effect of the extract, this diuretic action is purely transitory and is soon followed by an antidiuretic effect producing a striking oliguria. Abel's investigations are most convincing on this point.

There has been much discussion as to whether the various actions attributed to the posterior lobe of the pituitary are due to a single or several active principles. Führer,[9] in 1920, published the result of his work which led him to believe that there were four such principles in the pars nervosa that influenced the organs of circulation and respiration, the kidneys, intestines and uterus.

In 1924, Abel, Rouiller and Geiling[10] reported the isolation of the principle of the posterior lobe as a pituitary tartrate, which they found to possess the pressor, diuretic-antidiuretic, respiratory and melanophore-expanding actions known to be exerted by the extract of this lobe. They showed that this salt, when injected in solution subcutaneously, had the same antidiuretic action as pituitrin possesses in the treatment of patients suffering from diabetes insipidus. Abel believes that there is but one active principle in the posterior lobe and holds that all the pharmacologic actions attributable to the posterior lobe are possessed by his tartrate.

On the other hand, Kamm, Aldrich, Grote, Rowe and Bugbee,[11] following up the work of Dudley[12] in England, claimed in 1928 to have separated two active principles from the posterior lobe, one having a pressor, and the other an oxytocic action, and which they respectively call vasopressin and oxytocin. It is interesting to note that Gargill, Gilligan and Blumgart,[13] in studying the antidiuretic effect of these two principles on normal individuals and in 2 cases of diabetes insipidus, found that it was the vasopressin only that possessed this action.

Whether there is more than one active principle in the posterior lobe of the pituitary or not appears to be as yet unsettled. The experimental work of Abel on his tartrate salt seems so convincing, however, that it will probably be shown that his unity conception will be later confirmed.

How pituitrin exerts its effect is not definitely known. Stehle,[14] as a result of his experimental studies, offers the following hypothesis of its diuretic-antidiuretic action:

"Assuming that the capacity of the tissues to retain water is a function of the electrolyte content or ion balance of the tissues, we might regard the presence or absence of pituitary extract as entailing the following consequences. Pituitary administration causes the tissues to lose more potassium than sodium. This disturbance increases the capacity of the tissues to retain water, hence the antidiuretic effect. Absence or lack of pituitary secretion allows the reverse phenomenon to occur. That is, potassium may accumulate to a greater extent than usual. This decreases the capacity of the

tissues to retain water, hence the diuresis and thirst of diabetes insipidus. It is not to be understood that sodium and potassium are necessarily the only elements involved. They are singled out because definite information extends to them only aside from a slight knowledge of the phosphorus, calcium and magnesium excretion.

"The diuretic effect of pituitary extract offers no point contrary to the hypothesis suggested. As a result of the necessity to excrete the potassium and sodium discharged into the blood there may be some competition between the tissues and kidney for water. In this case while the tissues are probably doing their best to retain water the kidney succeeds in obtaining enough to eliminate the salts brought to it. It must be remembered that the urine of pituitary diuresis is a concentrated urine with regard to its salt content. It contains as much as 1 per cent of chlorin, or three times as much as the blood serum of the dog.

"In conclusion it seems worth while to suggest that some of the pharmacological actions of pituitary extract may be due to alterations in the quantities or interrelationships of electrolytes in the tissues."

That posterior-lobe extract possesses a remarkable influence on the regulation of water metabolism in man and animals seems without dispute. Some investigators hold that, when used therapeutically, it exerts its influence in diminishing urinary output merely as an effective pharmacologic agent, in a manner analogous to the action of the members of the theobromin series in producing diuresis. Others, on the contrary, maintain that it exerts its effect through its action as a hormone. In discussing the functions of the posterior lobe of the pituitary Abel says, "One of these functions which is probably exercised continuously under normal conditions, but a diminished supply of which in the circulating blood leads to diabetes insipidus, manifestly has to do with the mechanism of water retention and transportation in the body."

Since 1912 when Frank first attracted attention to the relationship between the pituitary and diabetes insipidus in reporting his gun-shot case, and since 1913 when von den Velden and Farini directed attention to the antidiuretic action of extract of the posterior lobe, the literature has contained numerous reports of diabetes insipidus associated with pituitary tumors. The association of dystrophia adiposogenitalis and diabetes insipidus or polyuria has been several times recorded. It is not surprising, therefore, that the view that diabetes insipidus is due to disturbed function of the posterior lobe of the pituitary has been the one that has chiefly prevailed during the intervening years, especially when we consider that extract of this lobe is the most effective remedy we possess for the relief of the polyuria at the present time. An argument advanced against this conception, however, exists in the fact that many tumors of the pituitary have been reported in which the

symptom-complex of diabetes insipidus was absent. Acromegaly without diabetes insipidus, for instance, is very common. Abel, who supports the pituitary conception, has found that he has been able to isolate his pituitary tartrate, although in small quantities, from the tissues of the hypothalamic region, and offers the suggestion that when diabetes insipidus is not present in destructive pituitary tumors, there may be sufficient of the extract present in the hypothalamus to maintain normal water metabolism in the individual.

Although, since 1912, the view that diabetes insipidus is a result of disturbed function of the posterior lobe of the pituitary gland, dependent usually on the effects of a pituitary tumor, has been the one most generally supported, yet there are many investigators who contend that no direct relationship between the two exists. The opponents of this conception are those, who, on experimental and clinical grounds, believe that diabetes insipidus is purely of nervous origin and dependent upon lesions involving one or more structures comprising the hypothalamus.

Before presenting this evidence, a brief statement of the anatomical relationship of the hypothalamus and hypophysis may be instructive. The hypothalamus occupies the base of the brain immediately above the hypophysis and its infundibular stalk. It includes the subthalamic tegmental region and the structures forming the greater part of the floor of the third ventricle, viz., the corpora mammillaria, tuber cinereum, optic chiasma, and infundibulum.

The *corpora mammillaria* are two round white masses, each about the size of a small pea, and situated posterior to the infundibulum, and placed side by side below the gray substance of the floor of the third ventricle.

The *optic chiasma* is a flattened, somewhat quadralateral band of fibers, situated at the anterior part of the hypothalamic region at the junction of the floor and anterior walls of the third ventricle. It is in front and above the infundibulum.

The *tuber cinereum* is a hollow eminence of gray substance between the corpora mammillaria behind and the optic chiasma in front.

From the under surface of the tuber cinereum a hollow conical process, the *infundibulum*, projects downward and forward and is attached to the posterior lobe of the hypophysis by the infundibular stalk.

The extent of the brain substance comprising the hypothalamus is comparatively limited, and its close relationship to the pituitary explains how easily pituitary tumors gradually increasing in size and destroying the anterior and posterior clinoid processes of the sella could readily invade or compress the structures comprising it. The fact that the optic chiasma is a constituent part of the hypothalamus accounts for the occurrence of the bitemporal hemianopsia so frequently reported in diabetes insipidus accompanied by basilar tumors, gummata, or basilar luetic meningitis.

Erdheim,[15] a pathologist, of Vienna, writing in 1904 appears to have been the first to suggest on clinical grounds that the polyurias associated with organic brain lesions were actually dependent upon tumors involving the hypothalamus. It has been shown above that the pituitary conception of the origin of diabetes insipidus dates essentially from the year 1912, although Cushing had drawn attention to the polyurias in experimental hypophysectomies in 1910. As a result of experimental investigations doubt was very soon expressed concerning the pituitary origin of the disease, and evidence was advanced pointing to its being of nervous origin and dependent upon lesions in the hypothalamus just above the pituitary.

Camus and Roussy[16] were the first to investigate this problem experimentally. In 1913 they reported to the Société de Biologie that they had been able to produce transitory polyuria by puncturing the hypothalamus of dogs through the sphenoidal bone with a heated drill. In one dog a permanent polyuria and in addition adiposogenital dystrophy had resulted. Their report stated that the lesion lay in front of the infundibulum and involved the tuber cinereum.

These investigators continued their experiments[17] and in 1920 reported what seemed very conclusive evidence that the polyuria does not depend on a lesion of the pituitary by producing it in a dog from which the gland had been previously removed. Following the removal of the pituitary there was a transitory polyuria. More than a month later, after the polyuria had subsided, a second polyuria of equal intensity was produced by puncture of the tuber cinereum.

Aschner,[18] writing in 1916, obtained similar results to those of Camus' and Roussy's early researches and even claimed priority in these experiments. Confirmation was reported by Houssay and Hug,[19] in 1921.

Bailey and Bremer,[20] in 1921, reported from Cushing's Clinic a very careful piece of experimental work on dogs confirming the views of Camus and Roussy. With the technique used by the latter there was always risk of injury to the pituitary. By a special surgical technique Bailey and Bremer exposed the hypothalamus by the temporal route, which permitted an exposure of the whole region. The punctures of the hypothalamus could be made where desired, and the pituitary, being in plain view, could be carefully avoided. When the animals died or were sacrificed sections were made of the injured hypothalamus, and of the pituitary to make sure that the latter had not been damaged in the operation. In all of their thirteen dogs in which the hypothalamic puncture was performed there developed a polyuria which appeared in the first two days. According to the extent of the lesion it varied from a transient one, lasting from six to eight days, to an apparently permanent polyuria. It is interesting to note that in some of the dogs the physical effect of the puncture on the animals resembled that

following hypophysectomy. Lesions of the tuber cinereum produced in two dogs a cachexia hypophyseopriva with acute genital atrophy, and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each of these cases verified histologically. It is important to note that these researches confirmed the observations of Camus and Roussy to the effect that injury to the hypothalamus, in addition to causing polyuria, also, in some instances, resulted in the production of an adiposogenital syndrome, which has been supposed to be dependent on pituitary disturbance.

The experiments of Camus and Roussy and of Bailey and Bremer have been substantiated by Hanchett,[21] Curtis[22] and others.

Camus and Roussy hold that the tuber cinereum is the anatomic structure in the hypothalamus injury of which produces the polyuria. The experimental work of Helen Bourquin[23] would seem to indicate that polyuria can be induced by injuries of the corpora mammillaria, which she considers the site of the effective lesion causing polyuria. Dogs were used in the experiments and the injury to the mammillary bodies was induced by cauterizing them with an electric needle. She holds that it is an irritative phenomenon because the polyuria results from slight injury of the bodies, rather than by destruction, in which case it is not induced. She believes that the diuresis must be due to a substance produced in the mammillary bodies as a result of their irritation and which acts directly or indirectly as a diuretic. She failed to produce polyuria in dogs by removal of the hypophysis, but these same dogs developed a polyuria when their corpora mammillaria were irritated. As a result of her experiments she believes that the thirst of diabetes insipidus is secondary to the diuresis, for the diuresis develops in operated animals restricted to their average pre-operative water intake and quickly produces manifestations of desiccation in diabetic animals deprived of water. She is of the opinion that neither the autonomic nor somatic nervous system is concerned in the diuresis, for in her experimental dogs it ran its typical course after transection of the spinal cord at the level of the eighth cervical vertebra.

The experimental evidence, therefore, seems very conclusive that injuries to both the tuber cinereum and the corpora mammillaria in the hypothalamic region can cause a definite polyuria in dogs; that many experimenters have removed the posterior lobe of the pituitary without more than a transitory polyuria resulting; and that polyuria does occur in these hypohysectomized dogs when either the tuber cinereum or corpora mammillaria are injured or irritated.

In addition to this experimental evidence of the relationship between polyuria and lesions of the hypothalamus, a limited amount of clinical evidence has also accumulated in recent years. Fink[24] has collected from the literature 107 necropsies in cases of diabetes insipidus. In looking over the synopses of these cases it is interesting

to note that many of those showing disease of the pituitary also refer to associated involvement of some of the structures of the hypothalamus. The number of cases in which the lesion appeared to have been limited to the hypothalamus seemed very small. In fact, the writer could discover only 3. One of these is the often quoted case of Lhermitte,[25] published in 1922, in which a syphilitic lesion involved both the infundibulum and tuber cinereum. Babonniex and Lhermitte,[26] in 1925, reported another case of diabetes insipidus with syphilitic basilar meningitis and lesions in the infundibulum and tuber cinereum. Verron[27] reported a case following trauma in which there was a circumscribed necrosis of the infundibulum.

Since the appearance of Fink's paper, a case of diabetes insipidus was reported in 1928 by Elmer, Kedzierski and Scheps[28] in a patient who had a hypernephroma of the kidney with a metastasis in the hypothalamus. An embolus of malignant cells had blocked an artery causing a necrosis of the tuber cinereum. There was a pinhead sized adenoma in the anterior lobe of the hypophysis, which they considered had no bearing on the cause of the diabetes insipidus.

The comparative rarity of clean-cut cases of tumors of the hypothalamus without any evidences of involvement of the pituitary gland seems to justify the reporting of the following case:

Case Report.—O. H. (History No. 44676), male, married, a chauffeur, aged forty-three years, was admitted to the Church Home and Infirmary, November 9, 1927, complaining of intense pain in the lower part of the back and down the thighs, intense thirst and passage of enormous quantities of urine.

The family history was unimportant.

There was nothing of special importance in his previous history excepting that at twenty years of age he had contracted gonorrhea and that nine years ago he had had an attack of lumbago. He stated that his health had always been good up to the onset of his present illness. He had been employed as a chauffeur for several years.

The onset of his present illness began six months before admission, when he began to have some cough. In the last week of August he developed night sweats. On September 11 he had a slight pulmonary hemorrhage. The physician of the large corporation for which he worked, suspecting pulmonary tuberculosis, arranged for his admission to the State Tuberculosis Sanitarium, at Sabillasville, Maryland, where he remained for about nine weeks previous to his admission to the Church Home and Infirmary. Two weeks previous to his admission to the latter institution he began to have severe pains in the lumbar region and down the outer aspect of the thighs. About this time he also developed intense thirst and marked polyuria. Although the patient was thought to have tuberculosis at the sanitarium, no tubercle bacilli were ever found in his sputum. Recently he had noticed a projecting lump over the left temporal region of the skull. He had lost 30 pounds in the last six months. The pain in the back became so intense that Dr. V. F. Cullen, Superintendent of the sanitarium, advised the patient to return to Baltimore to consult Dr. G. E. Bennett to see if there were any orthopedic condition producing the lumbar and thigh pains. He left the sanitarium the morning of November 9 and on the train journey to Baltimore became delirious and very confused as to time and place.

When he arrived in Baltimore he had high fever, and, as his condition seemed so serious the company physician arranged for his admission to the hospital the same afternoon. When Dr. Bennett saw him he realized that the condition was not essentially an orthopedic one and asked the writer to see the patient in consultation.

Physical Examination. The patient was seen on November 10, 1927, the day after admission. The following is a brief summary of the detailed note made at that time. The patient was complaining of intense pain in the lumbar region and down the thighs and took several long draughts of water during the examination. Moderately nourished. No special anemia or cyanosis. No jaundice.

Cranium. There was a prominence 4 cm. in diameter over the left frontotemporal region with a crater-like edge.

Eyes. No hyperthyroid features. Pupils unequal, the left being larger than the right. Scarcely any reaction to light but ready response to accommodation.

Pulse. Essentially normal. No palpable sclerosis.

Thorax. Diminished expansion throughout the entire right side. Lower intercostal spaces partially filled out.

Lungs: Right. Tactile fremitus diminished below the third rib in front and throughout the entire axillary region. Over this area there was marked dullness on percussion and increased resistance. The breath sounds were enfeebled and nowhere tubular. The voice sounds were enfeebled. No râles. Posteriorly, the tactile fremitus was exaggerated over the supraspinous fossa, diminished over the lower interscapular and absent over the subscapular area. There was marked dullness throughout with increased resistance. The breath sounds were markedly enfeebled throughout but nowhere tubular. There were a few medium moist râles over the supraspinous fossa. The vocal resonance was a little exaggerated above but almost absent below.

Left. Percussion and auscultation were essentially normal, excepting for a few moist râles at the base.

Heart. Sounds clear. By percussion the left border reached the mammillary line. There was no recognizable dullness over the manubrium.

Abdomen. No ascites. The liver dullness extended 3.5 cm. below the costal margin. Border not felt. No nodules felt on the surface. Spleen not felt. No masses elsewhere in abdomen.

There was no edema of the shins or feet.

Deep Reflexes. All were considerably exaggerated.

Superficial Reflexes. Normal.

Joints. No arthritis in joints of extremities.

Spine. In getting patient to sit up great pain in the lumbar region was experienced. The lumbar spine was almost immobile. There was no kyphosis or scoliosis.

Glandular System. No general glandular enlargement.

Impression. The following preliminary diagnosis was made at the time:

1. Examination of the chest, to be supplemented by Roentgen ray studies, without heart being displaced to the left suggests strongly tumor of the right lung and pleura.

2. Tuberculosis of lung and pleura to be excluded, but does not seem probable.

3. Tumor over left temporal bone suggests strongly a malignant metastasis, although a gumma has to be considered, as patient has anisocoria and a suggestive Argyll-Robertson pupil.

4. Has diabetes insipidus, which suggests pituitary involvement due to a metastasis or gumma. Involvement of the hypothalamic region might

produce the polyuria and polydipsia. Has passed 8170 cc. in less than twenty-four hours since admission.

Subsequent Studies and Course. The fluid intake and urinary output were daily measured until patient's death on November 28, 1927. The urine was extremely pale, the specific gravity averaging 1.004. There was no albumin or sugar. Microscopically a few red blood and pus cells were noted. The highest urinary output was 10,940 cc. on November 13, and the highest fluid intake was 12,000 cc. on November 18. On November 13, when the urine output was 10,940 cc. surgical pituitrin, hypodermatically, was started. On November 14, the pituitrin injections were increased to twice daily and November 16 the urine had fallen to 5150 cc. Curiously enough on November 18 the urine rose to 9375 cc. and the fluid intake to 12,000 cc. Owing to this increase 1 cc. of pituitrin three times daily was ordered on November 19 and on this day the urine fell to 5500 cc. and the fluid intake to 7000 cc. On November 22 the urine and fluid measurements were respectively 4500 cc. and 5200 cc. The last dose of pituitrin was given on this date. From this date on there were further diminutions in output and intake but it was not possible to keep careful records as the patient was quite delirious and in a semistupor at times. For the twenty-four hours of November 27, the day before his death, the output was recorded as 1100 cc. and intake 2000 cc. The patient was delirious and in a semicoma for the last four days preceding his death, which occurred on November 28.

The blood count on November 10 was as follows: red blood cells 3,310,000; white blood cells, 11,040; hemoglobin not recorded. Differential count was essentially normal.

The blood Wassermann test was negative. A Roentgen ray of the cranium showed that the sella was of normal size and shape. There was also a defect in the left temporal bone at the site of the swelling. The Roentgen ray of the chest showed a dense shadow involving the whole of the right lung. A biopsy was done on the tumor over the left temporal region for purposes of diagnosis. The sections were studied by Dr. Fried, the hospital pathologist, who reported that the tumor was an alveolar carcinoma.

Autopsy. The autopsy was performed by Dr. Fried, the writer being present. Following is a brief summary: The right lung was completely involved by the cancer with metastases to the mediastinal and peribronchial glands. There were also metastases present in the liver, pancreas, the left temporal bone and brain.

Our interest, naturally, was centered in the brain findings. On opening the skull there was found a defect in the left temporal bone due to a tumor metastasis. The tumor had grown out under the left temporal muscle and extended inward causing compression, but not actual involvement of the left frontal lobe. There were no other nodules seen anywhere on the surface of the brain.

The base of the brain was very carefully studied *in situ*. There was absolutely no evidence of any tumor mass seen on the surface of the brain in the infundibular region. The pituitary body was normal in size and showed absolutely no evidence of metastatic involvement.

The brain was hardened before being sectioned. It was found that a tumor 3 cm. in diameter was present in the hypothalamus involving the infundibulum and tuber cinereum. It was not visible from the outside. There was no bulging at the base and there was no evidence of compression of the infundibular stalk. The tumor began immediately beneath the pia at the attachment of the infundibular stalk and extended upward into the substance of the hypothalamus a distance of 3 cm. There was also a metastatic nodule about 1 cm. in diameter in the pons.

The histologic examination of the primary lung tumor, which probably began in a bronchus, as well as of the metastatic tumors of the hypothalamus and elsewhere showed it to be due to an alveolar carcinoma.

Discussion. From an anatomical standpoint the above case would appear to be a clear-cut instance in which the classical symptoms of diabetes insipidus were brought about by the development of a metastatic hypothalamic tumor secondary to a primary alveolar carcinoma of the lung, without any evidence of involvement or compression of the posterior lobe of the pituitary. The case would seem to be a strong argument against the view that diabetes insipidus is dependent upon the absence of the diuretic-antidiuretic pituitary hormone, since the presumption is that the formation of this hormone was not interfered with. There is now abundant experimental proof that the pituitary can be removed in dogs without diabetes insipidus developing, and it is believed that the polyurias resulting from the hypophysectomies in early experimental work were due to a concomitant injury of the structures in the hypothalamus. We have seen also that experimental injuries to the tuber cinereum and corpora mammillaria in dogs can be produced even in hypophysectomized dogs in which polyuria failed to develop after the pituitary was removed. It is contended by many that in those cases of diabetes insipidus reported as being dependent upon hypophysial disease there is also an associated injury of the hypothalamic tissue, and many of the case reports would seem to bear out this contention. How experimental lesions or tumors of the hypothalamus cause the diuresis is still an unsolved problem. While those supporting the hypothalamus origin of diabetes insipidus contend that the disease is of nervous origin, Bailey and Bremer believe that it is not dependent upon a supposed nervous or vascular regulation of the kidney. They found that it may be induced in animals whose kidneys have previously been denervated and, when present, persists after kidney denervation has been performed. Bourquin also found that neither the somatic nor autonomic nervous systems are concerned in the diuresis of experimental diabetes insipidus, as it runs its typical course after transection of the spinal cord at the level of the eighth cervical vertebra.

Do the structures in the hypothalamus contain a diuretic-antidiuretic hormone the prevention of the formation of which, as in the case of tumors in this region, leads to a disturbance of water metabolism and regulation? The investigations of Abel and his associates have shown that extracts of the infundibular region show this pituitary tartrate salt in small amount, and Abel advances the view that the failure of diabetes insipidus to develop in reported cases of pituitary disease may be due to the fact that there is sufficient of the diuretic-antidiuretic hormone in the hypothalamic tissues to prevent this symptom-complex from supervening. One can conceive that there might develop a compensatory increase in the production of this factor in the hypothalamus following earlier destruction of the function of the posterior lobe. The question has to be considered whether the pituitary tartrate, possessing diuretic-

antidiuretic properties, found in the hypothalamus by Abel is merely the secretion of the posterior lobe which is caught *en route* from the pituitary to the third ventricle, whence it eventually enters the circulation. Sato[29] in 1928 confirmed Abel's findings that the hypothalamus contains a substance which has an oxytocic action and also demonstrated the presence of a substance that possessed diuretic-antidiuretic properties similar to those of the posterior lobe of the hypophysis. He found that the whole of the tuber cinereum contains as much of the oxytocic and diuretic-antidiuretic substance as is contained in 1 to 2 or 2 to 4 mg. of the posterior lobe of the hypophysis. He believes that it exerts its effect through its hormonic action. It appears apparent to him that the diabetes insipidus that supervenes after destruction of the tuber cinereum is due to the fact that this diuretic-antidiuretic hormone is no longer formed.

It will be seen then that even though we may assume that lesions of the hypothalamus (tuber cinereum and corpora mammillaria) may cause diabetes insipidus, there are two views held by investigators as to how it is brought about. According to one view, the mechanism is through the nervous system—the nervous origin of the disease, but it is hard to explain the disease on this basis when it is found that it develops in experimental animals with lesions of the hypothalamus even after the kidneys have been denervated or after complete transection of the cervical cord. According to the other view it is due to the failure of the tuber cinereum or corpora mammillaria to produce a specific diuretic-antidiuretic hormone. The question should also be raised here as to whether tumors of the hypothalamus associated with diabetes insipidus may cause an interference of the transport of the diuretic-antidiuretic hormone from the posterior pituitary lobe to the third ventricle.

The possible interrelationship between the posterior lobe of the pituitary and the structures in the hypothalamus in connection with the etiology of diabetes insipidus is further complicated by the interesting fact that it now seems quite certain that these two structures are linked up by nerve fibers. Reference has already been made to the fact that Cajal and Cushing have demonstrated such fibers. An interesting observation has been made by Loewy[30] who destroyed the posterior lobe of the hypophysis in animals, and after from ten to fourteen days examined the tuber cinereum in serial sections. He found degeneration of the nucleus paraopticus and injured cells in the tuber cinereum (ganglion parahypophysios). The cells of these nuclei send out fibers which pass through the infundibulum to the posterior lobe of the hypophysis thus forming a united system, the injury of any portion of which, he believes may cause diabetes insipidus. Similar results were found by Clara Kary[31] who found axis cylinder fibers and only a few glia cells in the infundibulum. She observed that injury to the infundibulum led to degenerative changes in the tuber cinereum.

In this connection, it is interesting to note that Cushing, in his Cameron Lecture of 1925, reported that by shrinking the brain by the Weed method and compressing the hypophysial stalk by placing a silver "clip" about it he was able in dogs to produce the same train of symptoms as were evoked by Bailey and Bremer in their experiments on the hypothalamus, viz., a prolonged polyuria with subsequent tendency to adiposity.

A recent research of Trendelenburg,[32] of Freiburg, in 1928, seems of the greatest importance in pointing toward a compensatory interrelationship between the posterior lobe of the pituitary and the tuber cinereum of the hypothalamic region. In his experiments on dogs he found that in the hypophysectomized animals there appeared in the tuber cinereum an increasing amount of an antidiuretic substance, which acts exactly as does the secretion of the posterior lobe of the pituitary, and which is present in the tuber cinereum of normal dogs in much smaller amounts. He finds that this also applies to the oxytocic effect. He believes that diabetes insipidus, at least in animals, is probably purely hormonic in origin, and that when the diuretic-antidiuretic hormone of the posterior lobe of the hypophysis is destroyed by disease there appears a vicarious assumption of function on the part of the tuber cinereum in producing this hormone, and that the diabetes insipidus only supervenes in hypophysectomized animals when the tuber cinereum is destroyed. In his opinion this theory satisfactorily explains the previously conflicting views held concerning the explanation of experimental diabetes insipidus in dogs.

Elmer, Kedzierski, and Scheps, who reported the case of diabetes insipidus, due to an embolic hypernephroma metastasis, causing necrosis of the tuber cinereum already referred to, give an interesting classification of diabetes insipidus from an etiologic standpoint based on the experimental, clinical and pathologic experience at the present time. The classification would appear to clear up many of the conflicting views concerning the disease in human individuals. Their classification is as follows:

(*a*) Cases due to destruction of the posterior lobe of the hypophysis. Here the posterior lobe extract fails entirely or only in part to sensitize the regulating centers for water and salt in the hypothalamus. In these cases pituitrin has a definite, though transitory, therapeutic effect, because the regulatory centers in the hypothalamus are intact.

(*b*) Cases due to destruction of the water- and salt-regulating centers in the hypothalamus. In these cases the secretion of the posterior lobe is still produced, but it cannot sensitize the hypothalamic centers because they are destroyed. In this group the pituitrin has no effect whatever, since the regulating centers in the hypothalamus are destroyed and are incapable of sensitization.

(*c*) Cases in which there is an interruption of the communicating

nerve fibers connecting the hypothalamus (tuber cinereum) and the posterior lobe of the hypophysis. This group, they state, is insufficiently understood and requires further investigation. The therapeutic effect of pituitrin is not stated in this group.

The authors believed that their case belonged to the second group. The case here reported would seem to fall in the same group, although there did seem to be a therapeutic response to pituitrin. They emphasize that all cases do not fall accurately into their three groups, since there may be several factors at work in individual cases.

It will be seen that there are very conflicting views concerning the etiology of diabetes insipidus. The case reported in this paper definitely belongs to the group in which the pathologic lesion is present in the hypothalamus without evidence of any organic disease of the pituitary. The fact that the tissues of the hypothalamus, particularly of the infundibulum and tuber cinereum, were involved, is significant in our own case, but it is difficult to understand how diabetes insipidus occurred with an intact posterior lobe of the pituitary unless the transport of its secretion was interfered with in its passage to the third ventricle. On the view that water metabolism is regulated by centers in the hypothalamus controlling water metabolism and salt excretion an explanation could be found, but the analysis of the literature, and the effect of pituitrin therapeutically in many cases, forces the writer to the conclusion that water metabolism is regulated by hormonic control, whether that hormone be produced in the posterior lobe of the pituitary or in the tuber cinereum or mammillary bodies.

The demonstration of nerve fibers connecting the tuber cinereum and the posterior lobe of the pituitary is rather significant and further complicates the problem from the standpoint of etiology. The possibility of the interruption of nervous impulse along these fibers has at least to be entertained as a factor in the etiology of diabetes insipidus. It is interesting in this connection to quote from a personal communication from Harvey Cushing dated September 10, 1928, in reply to a request as to his present views concerning the etiology of diabetes insipidus. "I am sending you a copy of my Cameron Lectures in which I ventilated myself on the subject to try and reconcile Bailey's and my somewhat divergent views. There is of course no question but that the centers lie in the hypothalamic region since nerves appear to descend and get lost in the pars nervosa. We see a lot of diabetes insipidus, a good deal of it postoperative, because we are dealing fairly often with suprasellar tumors in these days and there is no question but that the water metabolism upset comes from damage of the third ventricle."

Summary. 1. A case of diabetes insipidus due to an alveolar carcinoma of the hypothalamus, secondary to a primary carcinoma of the lung, and without an involvement of the pituitary, is reported.

2. The case would naturally tend to support the view held by many that the diabetes insipidus is due to disturbance of certain regulatory centers in the hypothalamus.

3. The studies supporting the pituitary and hypothalamic conception of the origin of the disease is reviewed.

4. Reference is made to the fact that it now seems amply demonstrated that there are definite nerve fibers connecting the tuber cinereum and the posterior lobe of the hypophysis.

5. The belief is expressed that, although there may be certain centers in the hypothalamus regulating water exchange in the body, the evidence seems very strong that disturbance of the action of a diuretic-antidiuretic hormone produced in the posterior lobe of the pituitary is a very important factor in the etiology of the disease, possibly by sensitizing these centers or by influencing their function.

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MIKULICZ'S DISEASE AND THE MIKULICZ SYNDROME.

By J. P. Crozer Griffith, M.D.,
PROFESSOR OF PEDIATRICS, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

In 1888, Mikulicz[1] discussed before a German medical society a case of the condition which has since been called by his name; and in a later publication[2] reported it in fuller detail. Even before this, there had been a few similar instances recorded and since then there have been many contributions and collections of reported cases made. Lane[3] estimates that from 1888 to 1922 more than 120 articles had been published on the subject. Not only the disease proper, as described by Mikulicz, has been discussed, but allied affections of the salivary and lachrymal glands have been studied, very similar in many clinical manifestations but perhaps of different etiology. To all these latter the title Mikulicz's syndrome may well be applied; or, if desired, this term may include all diseases showing the peculiar involvement of the lachrymal and salivary glands which have been under consideration.

Yet all these conditions are still of uncommon enough occurrence to warrant the report of two additional cases, one of them apparently a genuine instance of the condition originally described by Mikulicz, the other of an entirely different pathological nature, being a manifestation of leukemia, but simulating the first case clinically in many important particulars. The study of Mikulicz's disease proper is of especial interest as bearing upon the possible influence of tuberculosis in producing the symptoms.

Case Reports. Case I.—Mabel J., aged nine years when admitted to the Children's Hospital of Philadelphia, April 25, 1924. Her previous health had been good except for the occurrence of measles and occasional colds. A little over six months before admission the upper lids of both eyes had become swollen and had remained so. About a week later swelling developed in the region of both parotid glands. She continued to feel well and to play about in her usual good condition. There had been no pain and no disturbance of the lachrymal or the salivary secretion.

Condition in the Hospital. She was a well-developed mulatto girl. The upper eye-lids seemed swollen, but on everting the lids this appearance was found due to a hard, lobulated, red mass, about 1 to 1½ cm. long, attached on the outer portion to the upper lid. The tonsils were only slightly enlarged. Swelling over both parotid regions extended downward to shortly below the angle of the jaw and backward to a little behind the lobes of the ears. The swelling was not movable or tender, and there was no pain on opening the mouth. There was some enlargement of the glands beneath the body of the jaw, probably due to involvement of the submaxillary salivary glands. The cervical lymphatic glands did not seem to be affected. There was a small gland in the left axilla and one in each groin. The liver did not appear to be enlarged. The spleen could not be felt distinctly. The Roentgen ray examination of the chest and skull (Dr. Ralph Bromer) did not

indicate the existence of any pathological condition. The Wassermann test was negative, as was the examination of the urine and the cutaneous and intracutaneous tests for the presence of tuberculosis. Studies of the blood on several occasions gave the following results:

TABLE I.—BLOOD PICTURE OF CASE.

	R.B.C.	Hgb.	Lcts.	Neutroph.	Lymph.	Large mono.	Trans.	Eosin.	Basoph.
April 26	5,160,000	77	5700	43	49	3	3	1	1
May 22	....	..	7100	42	44	1	2	10	1
June 14	....	..	7900	69	19	2	7	3	

The child was removed from the hospital on August 27, 1924. The accompanying photograph (Fig. 1) gives a good picture of her appearance. While in the hospital the patient received systematic Roentgen ray exposure of the parotid glands, but without noticeable effect. On June 3, a considerable portion of the left lachyrmal gland was removed and studied histologically.

Histological Report (Dr. A. Waltz): "Sections made from the lachrymal gland show a marked alteration of the glandular structure. There are comparatively broad bands of fibrous tissue dividing the gland into irregular but distinct lobules. These lobules for the most part contain single or conglomerate tubercles, which show the typical central area of epithelioid cells, with numerous giant cells surrounded by a zone of small round cells, but practically without necrotic areas. A few of the lobules contain remnants of glandular elements and large numbers of small round cells.

"The process is typical of tuberculosis, except that with such a general involvement of the gland one would expect more necrotic material and probably less fibrosis. However, no tubercle bacilli could be found by special staining methods, neither could tuberculosis be produced in guinea pigs by subcutaneous inoculation with glandular tissue" (Fig. 2).

This case may be called a typical instance of Mikulicz's disease proper, not dependent upon leukemia or any other condition of the blood, and without positive evidence of the existence of tuberculosis. The relationship to this latter disease will be referred to again.

CASE II.—Carolyn R., aged eight years, referred to me by Dr. Pursell of Phillipsburg, N. J., was admitted to the Children's Ward of the Hospital of the University of Pennsylvania, April 2, 1922. The child developed symptoms of Friedreich's ataxia when about two years of age. This condition very gradually grew worse, but gave little trouble until four or five months before admission. About this time swelling appeared in the "glands of the neck" together with some irregular fever. She had been growing thin and weak. Two months before admission a great enlargement of the spleen was discovered by Dr. Pursell, who had been called in on account of a severe febrile attack. On admission to the hospital, the child looked and seemed ill. There were the usual symptoms of Friedreich's ataxia, which need not be detailed. The upper eye-lids appeared swollen, and the parotid glands were large and hard. The cervical and submaxillary lymphatic glands were enlarged and somewhat matted. Radiographic examination showed some evidence of involvement of the mediastinal glands. The spleen was much enlarged and hard, extending to the right

FIG. 1.—Mabel J. Showing the enlargement of the lachrymal and parotid glands.

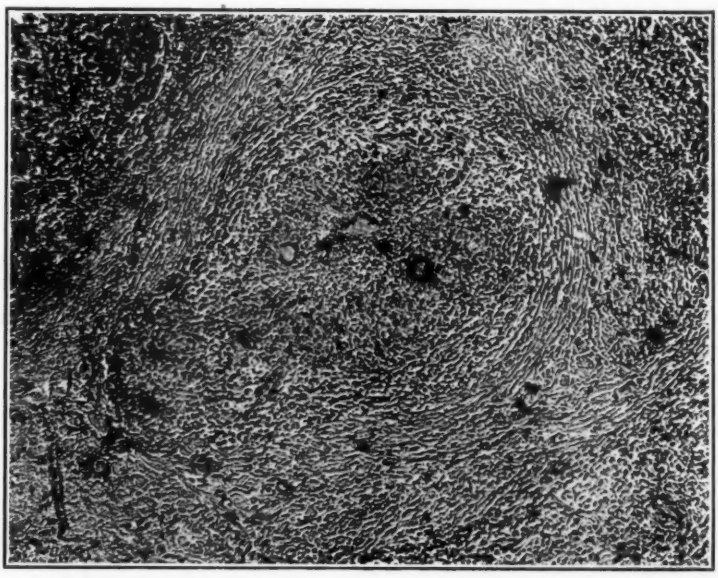

FIG. 2.—Photomicrograph (Case I) with central portion showing a typical tubercle histologically. Collection of epithelioid and giant cells with the usual areola of small round cells. Broad fibrous bands separate this tubercle from the rest of the section, giving a lobular appearance. The upper left area shows remnants of glandular elements and infiltration with numerous small round cells.

FIG. 3.—Case II, Carolyn R. Mikulicz's syndrome dependent upon leukemia.

of the median line three fingers' breadth below the costal margin. Several small purpuric spots were found on the left calf. The urine exhibited a trace of albumin. Another examination of the child a little later made it evident that the apparent swelling of the eye-lids was due to enlargement of the lachrymal glands on each side. Repeated examinations of the blood were made with the following results:

TABLE II.—BLOOD PICTURE OF CASE II.

	R.B.C.	Hgb.	Lcts.	Polys.	Mononuc.	Trans.	Lymph.	
April 22	2,080,000	42	340,000	2.0	3	0	95.0	Some anisocytosis. No nucleated reds. No myelocytes; most of the lymphocytes a little larger than usual but not sufficiently to determine from a laboratory point of view whether the case is of the acute or chronic type. (Dr. Cope.)
May 1	1,780,000	37	190,000	4.0	1	0	94.0	1 myelocyte, 1 normoblast in 20 w.b.c.
May 10	1,220,000	25	757,000	8.0	3	1	87.0	1 myelocyte; no nucleated red cells.
May 17	1,100,000	17	600,000	3.5	2	0	94.5	1 myelocyte, 1 nucleated red in 20.

The patient was removed from the hospital May 24, against advice, and died on the following day. While in the hospital, she had frequent nosebleeds. The eye-ground of the right eye exhibited many hemorrhages. Roentgen ray treatment of the bones of the body was systematically applied, but without benefit. The temperature ran an irregular febrile course. The accompanying photograph (Fig. 3) gives a good illustration of the appearance of the patient.

No autopsy was obtained in this case, yet even without this the diagnosis is clearly indicative of involvement of the parotid and lachrymal glands as a part of a general lymphocytic leukemia.

Comment. In view of the numerous valuable critical studies of the subject that have appeared in the years since Mikulicz made his contribution, no extensive review of the literature will be attempted. For further information regarding it one may consult the published papers of, among others, Howard,[4] Thursfield,[5] Igersheimer and Pöllot,[6] Hochschild,[7] Marsh,[8] Schaffer and Jacobsen,[9] Hamburger and Schaffer.[10] A brief synopsis of what is known of the disease may not be amiss.

The disorder as described by Mikulicz consists of a chronic symmetrical enlargement of the lachrymal and salivary glands, beginning in the lachrymal glands and perhaps limited to them, but usually gradually extending. The swelling is hard, painless and apparently noninflammatory. There is no disturbance of the lachrymal or salivary secretion and the general health is not affected. The author emphasized the nonparticipation of the lymphatic glands in the process, and the lack of alteration of the blood. He could discover no cause for the condition, but believed it was an

infection of some sort. Pathologic study of a portion of the lachrymal gland which had been removed revealed a widespread infiltration with round cells suggesting lymphadenomatous tissue.

Later experience of other investigators has shown that there is a number of other conditions with clinical manifestations in the lachrymal and salivary glands like those of Mikulicz's disease proper but with differences in other respects. It does not seem reasonable to base a sharp distinction on the existence, or lack of it, of moderate enlargement of some of the lymphatic glands; first, because the pathological process in the diseased salivary glands may well have its origin in some of the small lymphoid nodules which are naturally present, and consequently involvement of the lymphatic tissue elsewhere might well be expected; and, second, because moderate enlargement of the lymphatic glands in different parts of the body is of such common occurrence that its association with the salivary disorder may easily be merely a coincidental one.

Regarding the pathologic anatomy of the affected glands in Mikulicz's disease it has been found that there is a great lack of uniformity in the histologic changes which occur. This will be referred to later. Further, it has been claimed by Howard and others that there are a whole series of cases which form links from one variety of disorder of the salivary glands to other much more widespread infections, such as leukemia. This does not, however, appear to be definitely proven, and Schaffer and Jacobsen contend that it is not the case.

It is evident, then, that the relationship of the different forms of Mikulicz's syndrome to each other, the etiology, and the pathologic anatomy are far from being entirely clear. Nevertheless for the purpose of study some classification is needed. There have been a number of attempts at this. Howard has divided the syndrome into Mikulicz's disease proper, pseudoleukemia and leukemia. Thursfield's classification is rather more elaborate. That of Schaffer and Jacobsen, based upon the latter, is probably as convenient as any. These last authors divide the syndrome into:

1. MIKULICZ'S DISEASE.
   - (*a*) Familial.
   - (*b*) Mikulicz's disease proper.
2. MIKULICZ'S SYNDROME.
   - (*a*) Leukemia.
   - (*b*) Tuberculosis.
   - (*c*) Syphilis (?).
   - (*d*) Lymphosarcoma.
   - (*e*) Toxic.
     1. Lead.
     2. Iodids, etc.
   - (*f*) Gout.
   - (*g*) Febris uveoparotidea subchronica.

There are in addition some acute and some relapsing forms to which no reference is made here.

As concerns the various forms mentioned, the first is a congenital familial affection very rarely seen. Quincke[11] made a brief reference to a family in which several cases had been observed, and Léri and Gutmann[12] reported another instance of familial occurrence. The symptoms are those of the ordinary disease. A case said to be of this nature is reported by Laffolley[13] but it is doubtful whether it properly belongs in this category.

Mikulicz's disease proper is that as orginally described by Mikulicz, the cause of which is unknown. My first case is a very typical instance of this. The symptoms have already been mentioned. As stated earlier it does not seem necessary to exclude all cases in which there is some moderate enlargement of the lymphatic glands.

Considering the Mikulicz syndrome, as apart from the forms already mentioned, that due to leukemia is well illustrated in my second case. In this form the involvement of the salivary and lachrymal glands is only one manifestation of the general leukemic process. It is, however, distinctly a rare one.

The influence of tuberculosis has been much discussed. A valuable contribution upon the subject was that of Igersheimer and Pöllot, who published the report of a case of enlargement of the lachrymal and submaxillary salivary glands. The histologic examination of the lachrymal glands showed a round-celled infiltration, small nodules of epithelioid cells and numerous giant cells, with an overgrowth of connective tissue, producing an appearance, which, they say, would, without hesitation, have been diagnosed as tuberculosis. There were, however, no tubercle bacilli found, repeated subcutaneous injections of the patient with tuberculin gave negative results and the introduction of portions of the excised gland into the anterior chamber of the eye of two rabbits and into the peritoneal cavity of two guinea pigs was entirely without result. The authors then enter upon a careful, thorough and critical discussion of the problem. In view of the importance of the subject this may well be reviewed here somewhat in detail. They raise the question whether cases of Mikulicz's disease with the histologic picture of tuberculosis are in reality tuberculous in spite of the absence of all positive proof of the existence of tubercle bacilli, or whether there exist other causes capable of developing an inflammatory condition which may produce a histologic picture resembling that of tuberculosis. To elucidate this they publish a valuable clinical review of all the reported cases, 44 in all, of enlargement of the lachrymal glands, with or without involvement of the parotids, which had been regarded by the reporters as possibly or certainly tuberculosis, or which had exhibited histologic changes of the glands resembling those seen in their own case and indicating a tuberculous lesion. Only 3 cases were found in which they could regard the

process as certainly tuberculous, and 2 others in which the diagnosis seemed probable. It may be said here that one of the 3 cases, that of Krailsheimer[14] is reported by the author as showing tubercles and giant cells, but no report is made of the finding of tubercle bacilli. A translation of this article[15] in an English journal apparently incorrectly says "tubercle bacilli" instead of "tubercles." This appears to have caused some confusion. The case cannot be regarded as a proven one of tuberculosis. Igersheimer and Pöllot conclude that tuberculosis has, as a rule, nothing to do with the production of Mikulicz's disease, although in some cases the tubercle bacillus is capable of producing the condition. They maintain, further, that the presence of epithelioid tubercles and of giant cells in the gland is no positive proof of the existence of tuberculosis there. The condition in my first case would seem to be entirely in support of this view. Thursfield, among others, also expresses the opinion that although tuberculosis can produce Mikulicz's disease the great majority of the cases have no connection with this cause. Bearing upon this conclusion especial attention might be called, for instance, to the case of van Duyse[16] in which epithelioid cells and typical giant cells were found in an excised portion of the lachrymal gland. The tumors, however, disappeared in six weeks under the administration of potassium iodid. A case of Fleischer[17] was very similar to this, bioscopic examination of the lachrymal gland strongly indicating tuberculosis. Baumgarten who examined the slides admitted the similarity to the histologic picture of tuberculosis, but stated that a positive diagnosis could be made only by animal inoculation or by the finding of the bacillus. The swelling in the glands in Fleischer's case disappeared entirely within three months. The case of Külbs[18] suggested tuberculosis in many particulars on histologic examination, although autopsy made some time later, after suicide, revealed no evidence of tuberculosis anywhere in the body. A much more recent review of the literature by Marsh failed to add any to the three instances of tuberculosis regarded by Igersheimer and Pöllot as certain. In Marsh's own patient the tumors were all of decided hardness, the tuberculin reaction was positive, miliary tubercles and epithelioid nodules with giant cells were discovered at the time of microscopic examination, but no tubercle bacilli were found and there was no caseation. No inoculation tests were made. Later the involved salivary glands resolved to a great degree. The patient was suspected of having pulmonary tuberculosis but this was never proven. In a patient reported by Scales[19] there was involvement of the lachrymal and parotid glands. The tuberculin test was negative. Microscopic studies of a removed lachrymal gland showed many tubercles, giant cells, and a round-celled infiltration; no necrosis or tubercle bacilli. Various pathologists examined the specimen with a diversity of opinions. Later the swelling of the remaining lachrymal gland

practically disappeared and there was a marked decrease in the size of the parotids.

The influence of syphilis is very uncertain. Some cases of Mikulicz's syndrome have improved under antisyphilitic treatment; but this is not definite proof that there were syphilitic. There may be an actual connection but it is not proven.

Sarcoma has repeatedly been described as involving salivary glands and the lymphatic glands as well.

Finally there is the curious condition described by Heerfordt[20] under the title of "Febris uveoparotidea subchronica," and later by a few other observers including Hamburger and Schaffer, in which iridocyclitis is the prominent symptom, associated with parotid enlargement and often with involvement of the other salivary glands, and of lymphatic glands as well, and in some cases attended by a polyneuritis. The relationships of this disorder are varied and obscure.

Regarding the influence of age, Mikulicz's patient was an adult. An analysis of Howard's series of 55 cases of Mikulicz's disease proper show that 7 were not over fifteen years of age, and of these 2 were not over six years. Taking Mikulicz's syndrome as a whole, including the 55 cases mentioned, there were 81, with 17 not over fifteen years of age, 6 of these being not over six years. I do not know that there has been any collective study of the age incidence since the date of Howard's contribution, but this is sufficient indication that although the syndrome is more commonly observed after childhood it is comparatively not infrequent during early life.

The cause of the enlargement in Mikulicz's disease proper is unknown. Thursfield suggests that it is probably dependent upon irritative processes in the pharynx, mouth and conjunctiva. In other forms of Mikulicz's syndrome it has to do with the original cause of the general condition.

In the matter of the pathologic anatomy of the disease, it would seem that the primary change in the glands consists of an extensive deposit of small round cells which more or less displace and often compress the glandular parenchyma. These cells may be an infiltration of leukocytes, or a proliferation of the nests of lymphadenoid tissue normally present in the glands. These changes are, however, not uniformly or solely seen, as already pointed out. Sometimes considerable new-formed connective tissue has been discovered, indicating a chronic inflammation, and in a comparatively large number of the cases in which histologic studies have been made a condition strongly suggesting the changes seen in tuberculosis has been found. By some observers giant cells, apparently genuine, have been described, and by others these formations have been designated as pseudo giant cells, or by other terms. There is rarely any evidence of caseation. The hardness of the gland, the tendency to decided connective tissue overgrowth, and the

absence of caseation are not in accord with the typical picture of tuberculosis, but in other respects the similarity is marked.

With regard to the prognosis and treatment, these depend upon the nature of the case. In the secondary cases, they are entirely that of the primary disease. It is noteworthy that even in such cases the treatment of the enlarged salivary glands by Roentgen ray or radium may at times reduce the swelling; but the general disease may go on to a fatal issue. In my own leukemic case Roentgen ray treatment was entirely without effect.

In the cases of Mikulicz's disease proper the prognosis is uncertain, but not entirely unfavorable. Thursfield states that "one to five years as a rule releases the patient" from the discomfort and disfigurement. Sometimes the swelling has disappeared during the occurrence of some general infection, to reappear later. The use of radium or Roentgen ray in treatment of the parotid swelling has had remarkably good results in some instances, and in others the enlargement has entirely or largely vanished without satisfactory cause being known. In my own case Roentgen ray treatment was without benefit. Surgical removal of the enlarged lachrymal glands has been done repeatedly, and with good results in relieving the interference with vision and the disfigurement.

Summary. Two cases of Mikulicz's syndrome are reported; one dependent upon leukemia, the other, which might be called Mikulicz's disease proper, having no discoverable cause. The symptoms and lesions are discussed with special reference to the influence of tuberculosis. A study of some of the literature as well as the bioscopic examination in my own case supports the conclusions of others, viz., that although tuberculosis may be a cause of Mikulicz's disease, it is rarely so, and that even a histologic appearance in the glands which strongly suggests tuberculosis is not a positive proof that the disease is present.

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REVIEWS.

MEDICINE: ITS CONTRIBUTION TO CIVILIZATION. By EDWARD B. VEDDER, A.M., M.D., D.Sc., F.A.C.S., Lieut-Col., M. C., U.S.A. Pp. 388. Baltimore: Williams & Wilkins Company, 1929. Price, $5.00.

IN 1800, the average length of life in the United States was thirty-three years. In 1924, the expectation of life at birth had increased to 58.1 years. These few figures well exemplify the achievements of medical science in the treatment and prevention of disease. New discoveries will lead to still greater triumphs, but in the meantime much can be gained by the widespread application of knowledge already at hand, particularly as regards personal hygiene and the correction of defects found in periodic health examinations. To accomplish this, "medicine with its ideals and achievements must be popularized." In this book, Colonel Vedder presents the more important facts of preventive medicine for the layman. Part I discusses the causes of disease with chapters on predisposing causes, infectious diseases, nutrition and nutritional diseases, diseases of the glands of internal secretion and the degenerative diseases. Part II takes up the present accomplishment in disease prevention and the problems of the future, with chapters on the conquest of disease, the cancer problem, and modern preventive medicine. The book is well written and by one eminently qualified. The terminology is for the most part intelligible for the layman, but a glossary might perhaps have been added to advantage. Thus the term "filterable virus" is used a number of times previously but is not defined until page 75. As an example of medical progress in the short time since the book was written the Reviewer noted the statement concerning ephedrin: "something of a medical curiosity and not readily obtainable:" today one of the commoner drugs and beginning to be produced synthetically. R. K.

PHYSICIAN AND PATIENT: PERSONAL CARE. Edited by L. EUGENE EMERSON. Pp. 244. Cambridge: Harvard University Press, 1929. Price, $2.50.

YEARS ago, the young medical student through his preceptor early became aware of the human relations between doctor and patient and how large a part they play in the art of medicine.

Nowadays, when the Science of Medicine has so filled the student's hours, he is not sufficiently reminded that the practice of medicine has to do with persons as well as diseases. In recognition of this gap in medical teaching, a series of lectures has been given during recent years before the students of the Harvard Medical School by men eminent in the profession. One of these lectures (The Care of the Patient, by Francis W. Peabody, M.D.) has already appeared in print and has been reviewed in these columns. The present volume includes ten lectures: "Some of the Human Relations of Doctor and Patient" (Dr. David L. Edsall); "The Care of Patients: Its Psychological Aspects" (Dr. C. F. Martin); "The Medical Education of Jones; by Smith" (Dr. W. S. Thayer;) "The Significance of Illness" (Dr. Austen Fox Riggs); "Some Psychological Observations by the Surgeon" (Dr. Lawrence K. Lunt); "The Care of the Aged," "The Care of the Dying." "Attention to Personality in Sex Hygiene" (Dr. Alfred Worcester). Every senior medical student should be required to read such a book, and should reread it in his intern year. But it could be read with profit by all physicians, by nurses and as the editor suggests, by "all who ever have been sick or ever have anything to do with the sick—pretty nearly everybody, in fact."

R. K.

Diagnosis and Treatment of Deformities in Infancy and Early Childhood. By M. F. Forrester-Brown, Surgeon, Bath, Somerset and Wilts Central Children's Orthopædic Hospital. Pp. 193; 79 illustrations, Oxford, England: Humphrey Milford, Oxford University Press, 1929. Price, $4.15.

This book is an exposition of principles of orthopedic surgery dealing with diagnosis and treatment, especially preventive. Operative treatment is purposely but briefly described. The book is particularly intended for the general practitioner, the physician interested in infant and child welfare work and the school doctor. The author aptly points out the fact that they have the earliest and best opportunities to see such cases. To these, this book will be a valuable aid. The book is written in a clear and concise fashion and is well illustrated.

J. M.

The History of Hemostasis. By Samuel Clark Harvey, M.D., Professor of Surgery, Yale University, New Haven, Conn. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

"Reprinted, with additions" from the Annals of Medical History, this constitutes an interesting addition to Hoeber's

biographical and topical series that has already frequently been alluded to in these columns. Starting from the Ebers papyrus, the author follows man's efforts to control hemorrhage through the classic periods and that of Western Europe to Paris, Morel and Lister, with especial attention to the tourniquet, hemostat and ligature. Without adding to the sum of our knowledge of hemostasis, the book affords an hour or more of pleasant reading on an important surgical problem. E. K.

THE CYTOARCHITECTONICS OF THE HUMAN CEREBRAL CORTEX. BY CONSTANTIN VON ECONOMO. Professor of Neurology and Psychiatry, University of Vienna. Translated by Dr. S. Parker. Pp. 186; 61 illustrations, 46 of which are photographs. New York: Oxford University Press, American Branch, 1929. Price, $6.25.

NEW limits are given for the occipital, temporal and parietal lobes, and partly for the olfactory lobe. The cortex is composed of various laminæ, "each of which has probably a certain function in the physiological activity of the gray matter." A further subdivision gives different "areas" of which there are more than one hundred. The question in pathology is whether a certain disease causes laminal or areal changes. Amyotrophic lateral sclerosis shows an areal spread while paresis and senile dementia are selective. In the two latter, in Pick's disease, also in dementia precox and chronic alcoholism, it is the third lamina that is particularly involved.

N. Y.

DIAGNOSTIC METHODS AND INTERPRETATIONS IN INTERNAL MEDICINE. BY SAMUEL A. LOEWENBERG, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Jefferson Medical College. Pp. 1032; 547 illustrations. Philadelphia: F. A. Davis Company, 1929.

ANOTHER has been added to the long list of books dealing with diagnostic methods. This volume deals with the physical examination of the various systems, and contains chapters on the interpretation of laboratory findings, radiography, and special industrial and insurance examinations. Only too often the wide scope, which such a work necessitates, proves to be a pitfall for the author, and the immense amount of ground which must be covered results almost inevitably in superficiality. This has been the case in this instance, with the exception of the sections on the respiratory and cardiovascular systems, which have been thoroughly discussed. There are some careless statements and many obscure ones. It will not stand as an authoritative work. E. R.

TEXTBOOK OF CLINICAL NEUROLOGY. By M. NEUSTAEDTER, M.D., PH.D. Clinical Professor in Neurology, New York Polyclinic Medical School and Hospital. Formerly Lecturer in Neurology, University and Bellevue Hospital and Medical College. Pp. 602; 228 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $6.00.

SINCE this volume is written expressly for the medical student and the general practitioner, the conventional textbook arrangement is abandoned so that the symptomatology of each disease is given first.

The subject matter is practical and is clearly and concisely written. An illustration of this may be seen even where description is difficult, as in the comparatively recent and but seldom recognized disease of Schilder—encephalitis periaxialis diffusa.

In the chapters on poliomyelitis, encephalitis and tremors, a distinctly original tone is shown. With his own tremograph the author has made many tracings which are generously distributed throughout the text "and it appears that they always show definite characteristics, irrespective of their fineness or coarseness."

A feature of the book is that it is profusely illustrated, many of the figures are original and all are well chosen. The stated purpose of the volume is admirably fulfilled. N. Y.

THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE. By GEOFFREY BOURNE, M.D., M.R.C.P., and KENNETH STONE, M.D., M.R.C.P. Pp. 392; 10 illustrations. New York: Oxford University Press, American Branch, 1929.

THIS book represents a successful effort on the part of the authors to set down in compact form the clinical pathologic findings usually obtained in the study of disease. A short discussion concerning the pathologic origin is given at the beginning of the section for each disease. Then follows a list of the usual laboratory tests which may be useful in the diagnosis or as a guide in the treatment. Each test is described from the point of view of interpreting the results and of applying them in the diagnosis and treatment of the disease in question. When the procedure is simple and does not require elaborate apparatus, the technique is often briefly stated.

In some diseases suggestions as to treatment are given, usually measures which are suggested by the laboratory findings, that is, the administration of sera, vaccines, and so forth. Related prophylatic measures are also mentioned. At the end of most chapters a short bibliography is given.

The book is written for the practioner of medicine and records only the "accepted" tests, the choice of which is not always an easy

matter. Thus, in outlining tests of liver function, are given Fouchet's test, the van den Bergh test, levulose and galactose tolerance tests, and the glycuronic acid reaction. No mention is made of the tetrachlorphthalein test, Widal's "crise hemoclasique" or icterus index test. The significance of urobilin in the urine is said to be doubtful.

The volume is easily readable, and presents its subject in such a useful and practical way that it should prove a valuable aid to both practioner and student. L. F.

THE MODERN DANCE OF DEATH. By PEYTON ROUS. Pp. 51. Cambridge: The University Press, 1929.

To those who, often with justice to be sure, cavil at the style in which American medical scientists present their material, the author can be pointed out as a shining exception. And nowhere does this pleasant capability stand out better than in the Linacre lecture that this booklet presents. A sympathetic yet critical appreciation of the various Dances of Death so prevalent in Linacre's time precedes a thoughtful and artistically expressed consideration of various new and often unexpected aspects of pathologic physiology. These, brought about by man's rather sudden acquisition of operative and biologic control over his normal and morbid processes, show that Death's dancing partner is no longer passive as in the ancient prints. The physician's increasingly apparent duty, that of keeping old bodies fit, will thus produce a new Dance of Death, though the author is one with his old master, Warthin, in viewing much of the aging process as inevitable. E. K.

AN INDEX OF SYMPTOMATOLOGY. By VARIOUS WRITERS. Edited by H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Assistant Physician, St. Thomas' Hospital; Consulting Physician, Royal Northern Hospital. Pp. 710; 130 illustrations; 4 colored plates. New York: William Wood & Co., 1929. Price, $12.00.

IT is attempted in this work to give a definition and a brief description of the clinical picture of diseases, adequate for enabling the practitioner to recognize a fairly typical case. Written by twenty-six contributors, engaged in the practice of the various specialties, the work covers all the branches of medicine, surgery, gynecology and the special subjects. The material is presented by diseases or diagnoses, arranged alphabetically from "Abdominal Injuries" to "Yellow Fever." The descriptions are for the most

part well done. The illustrations are excellent. That omissions should occur in the first edition of a book covering so wide a field is not to be wondered at: it is indeed surprising that there are so few. Some that the Reviewer noted are: cervical rib, foreign bodies in the bronchial tree, inguinal granuloma, the relation at times existing between lung abscess and lung neoplasm, the work of Goldberger on the etiology of pellagra. The book should be valuable for quick and handy reference in diagnostic problems. R. K.

LABORATORY MANUAL OF THE DIVISION OF BACTERIOLOGY, PEKING UNION MEDICAL COLLEGE. Prepared under the direction of C. E. LIM, Peking Union Medical College. Pp. 154; 20 charts. Peking, China: Peking Union Medical College Press, 1929. Price, $1.50.

THIS book is a manual of the bacteriologic and serologic methods in use at the Peking Union Medical College Hospital. It is printed on a good grade of paper in easily read type, and is bound serviceably. There are a few inconsequential typographical and linguistic errors.

The contents include directions for all the common bacteriologic and serologic procedures, in most instances only one technique being given—their preferred method. This naturally is not in all instances the preferred method in all laboratories. The subject of protozoölogy is not included.

The directions are concise and easily followed.

It would have been well to include more detailed directions in some cases, as in the clearing of culture media, for instance.

The classification of bacteria is for the most part not carried very far, rather rough clinical classifications being followed—streptococci merely as hemolytic and nonhemolytic, for example.

There is a useful chapter upon the care of animals and cost of upkeep, such as is seldom found in the smaller books on laboratory methods. F. L. JR.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. Volume IV, Part II. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 241; 18 plates (full page). Baltimore, U. S. A.: The Williams & Wilkins Company, 1929.

VOLUME IV of these *Annals*, devoted to the pathogenic streptococci, is presented in two parts. The streptococci have been ex-

amined in relation to the different diseases with which they can be identified, and a separate monograph compiled on each disease. Part I (previously reviewed, see April, 1929, p. 576) contains four monographs. Part II, which consists of three monographs, deals with the rôle of the streptococci in acute suppurative arthritis and in chronic rheumatism, including rheumatoid arthritis and osteoarthritis. Rosenow's hypothesis of elective localization is also reviewed.

These monographs give a complete résumé of the researches which have been carried out since the beginnings of bacteriology, and are not confined to the streptococcal theories alone, but supply an account of most of the important views and theories held by various clinicians. The volume, therefore, comprises much information which should not only be of interest to the bacteriologist but to the clinician as well; it also contains a very large bibliography of over 1600 references, an author's index, and a very complete subject index.

Special attention is drawn to the original work of Warren Crowe on osteoarthritis and the author's simple new differential test for the streptococci. With Vol. III, Vol. IV, Part I (completed), and Vol. V, VI and VII (to be published), Vol IV, Part II is important as a unit in the proposed comprehensive study of pathogenic streptococci which will undoubtedly aid materially in identifying the great majority of the many varieties of streptococci. W. K.

BOOKS RECEIVED.

NEW BOOKS.

*Interns Handbook.** Under direction of M. S. Dooley, A.B., M.D. Pp. 235. Philadelphia: J. B. Lippincott Company, 1929. Price, $3.00.

*Surgical Diseases of the Thyroid Gland.** By E. M. Eberts, M.D. Pp. 238; 48 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $3.50.

*The Female Sex Hormone.** By Robert T. Frank, A.M., M.D., F.A.C.S. Pp. 338; 86 illustrations. Springfield, Ill: Charles C. Thomas, 1929. Price, $5.50.

La Terapia Epatica e le sue Applicazioni con Particolare Riguardo all'Anemia Perniciosa Series 1 *N.* 27.* By Paolo Introzzi. Pp. 74.

Medical Clinics of North America (Chicago Number) Vol. XIII, No. 2, *September*, 1929. Pp. 232; 61 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*What Everyone Ought to Know.** By Oliver T. Osborne, M.D. Pp. 313. Springfield, Ill: Charles C. Thomas, 1929. Price, $2.50.

* Reviews of titles followed by an asterisk will appear in a later number.

Oxford Monographs on Diagnosis and Treatment. Vol. V. Edited by HENRY A. CHRISTIAN, M.D., Sc.D. L.L.D. *The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract.** By ELMER H. FUNK, M.D. Pp. 618; 182 illustrations. New York: Oxford University Press, American Branch, 1929.

*The Layman Looks at Doctors.** By S. W. and J. T. PIERCE. Pp. 251. New York: Harcourt, Brace & Co., 1929. Price, $2.00.

Premiére Conférence Internationale de la Lumiére. Physique, Biologie, Therapeutique, Lousanne et Leysin, September 10–13, 1928. Pp. 543. Illustrated. Française, Paris: L'Expansion Scientifique, 1929. Price, 10 francs.

In the 8 seances and conferences are included some two score reports and communications by specialists of many nations, a number of whom are internationally known.

Progressive Medicine, Vol. III. September, 1929. Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 327. Illustrated. Philadelphia: Lea & Febiger, 1929.

*Tularemia.** By WALTER M. SIMPSON, M.S., M.D., F.A.C.P. Pp. 162; 55 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $5.00.

*The Doctor in Court.** By EDWARD HUNTINGTON WILLIAMS, M.D. Pp. 289. Baltimore: Williams & Wilkins Company, 1929.

NEW EDITIONS.

Text-book of Embryology. By F. R. BAILEY, A.M., M.D., and A. M. MILLER, A.M. Pp. 687; 529 illustrations. Fifth edition. New York: William Wood & Co., 1929. Price, $7.00.

Diseases of the Stomach. By MAX EINHORN, M.D. Pp. 593; 131 illustrations. Seventh edition. New York: William Wood & Co., 1929. Price, $6.00.

Practical Local Anesthesia and Its Surgical Technic. By ROBERT EMMETT FARR, M.D., F.A.C.S. Pp. 611; 284 illustrations. Second edition. Philadelphia: Lea & Febiger, 1929. Price, $9.00.

*The Nutrition of Healthy and Sick Infants and Children.** By E. NOBEL, C. PIRQUET and P. WAGNER. Translated by BENJAMIN M. GASUL, B.S., M.D. Pp. 243; 78 illustrations. Second revised edition. Philadelphia: F. A. Davis Company, 1929. Price, $3.50.

Clinical Medicine for Nurses. By PAUL H. RINGER, M.D. Pp. 330; 16 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1929. Price, $3.00.

Memoranda of Toxicology. By MAX TRUMPER, B.S., A.M., PH.D. Pp. 214. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1929.

*The Chemical Aspects of Immunity.** By H. GIDEON WELLS, PH.D., M.D. Pp. 286; second edition. Chicago: Chemical Catalogue Company, 1929. Price, $6.00.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Wassermann Reaction of Human Milk.—A comparison of blood and milk tests in 107 cases. It is obvious that examination of the milk of a puerperal patient affords a convenient method of determining the presence of syphilis. The only question that might arise would be whether or not the reaction with milk would be as exact as with blood serum. The first thought would be that the amount of fat in milk might in some way affect the reaction. That this is not the case is proven by a recent paper by JARCHO (*J. Lab. and Clin. Med.*, 1929, **14**, 1097), who shows that there is rather a close parallelism between the Wassermann reaction on the milk of puerperal women and the blood. One hundred and seven examinations were made and 95 per cent of the cases agreed in substance and there was exact qualitative-quantitative agreement in 89 per cent. Three times the milk was positive and the blood negative, while only twice was the blood positive and the milk negative. In addition to the convenience of obtaining material for examination, it is also true that the test should be practical for the testing of the milk of prospective wet nurses.

The Effect of Exercise on the Size of Normal Hearts and of Enlarged Hearts of Dogs.—For many years clinicians have been interested in the possibility of exercise producing changes in the heart. Long-continued exercise or training carried to excess will always produce a change in heart weight-body weight ratio. However, this statement does not apply to animals or men who have recently undergone a relatively short but severe form of exercise. STEWART (*J. Clin. Invest.*, 1929, **7**, 339), using somewhat different methods than have been employed in the past, has reopened the question and investigated the effect of exercise not only on the normal heart but on the heart of dogs in which lesions

of the mitral valve have been produced through operation. The experimental animals were taught to run on a treadmill. The hearts were Roentgen rayed according to a method described by the author two years ago. These Roentgen ray photographs were made before the dog began running on the treadmill, immediately afterward and after rest of an hour. The animals ran steadily from twenty to sixty minutes. In normal dogs there was a quite marked diminution in the size of the heart after the voluntary exercise. For example, in one dog immediately afterward there was a fall to 94.8 per cent of the initial size followed by a further decrease to 92.8 per cent. In dogs with already increased hearts in which systolic murmurs were present, figures comparable to those in the normal dog were obtained. The same statement holds true with the effect of exercise on the size of the heart in dogs who have been subjected to operation, but in which the valvular difficulty cannot be demonstrated. If, then, there was diminution in the size of both normal and enlarged hearts in which there was presumably no myocardial disease and no signs of heart failure, it is fair to assume that dilatation of the heart occurs only in that organ in which disease has produced changes in the myocardium.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

A Clinical Consideration of Urinary Antiseptics.—KAUFMAN (*J. Urol.*, 1929, **22**, 163) says that the general practitioner as a rule first sees the common forms of infection of the urinary tract. It is essential that he be familiar with the limits of general treatment. Treatment of urinary infection demands primarily recognition of the factor of drainage. Water is essential with certain physiologic aids in combating pyrexia, toxemia and renal failure. Urinary antiseptics serve an important purpose in the treatment of both acute and chronic infections. They are now clearly established on both scientific and clinical grounds.

On Dilatation of the Ureters and Hydronephrosis in Childhood.—MACMYN (*Brit. J. Urol.*, 1929, **2**, 150) claims that the condition is not common but may frequently be overlooked; and being unsuspected may rapidly reach a fatal termination. Its recognition is only possible after careful urologic investigation, which includes all the modern methods of examination at our disposal. The condition is marked by disorders of micturition, due to obstruction and superadded infection. A valvular obstruction in the posterior urethra is regarded as being more common than has been previously supposed and is held to account for many cases of dilatation of the urinary tract hitherto ascribed to other causes.

In postmortem examinations of cases where the obstruction is not at first apparent, a careful dissection of the urethra is essential. The whole urinary tract should be removed *en masse* for this purpose. The disease is especially liable to be associated with other congenital abnormalities, whether in the urinary tract or elsewhere in the same child. Modern methods of diagnosis favor a more early recognition of the disease and afford the urologist a better chance of success in its treatment.

Osteitis Fibrosa and Giant-cell Tumor.—GESCHICKTER and COPELAND (*Arch. Surg.*, 1929, **19**, 169) find that in an analysis of over 400 cases of tumor in the giant-cell group, a pathologic relationship was established between the bone cyst, giant-cell tumor of the long bones and skull, giant-cell epulis of the alveolar borders and giant-cell tumors of the tendon sheaths. The usual bone cyst occurring in the metaphyseal region of the long bones of young patients, was shown to be a healing phase of giant-cell tumor—a conclusion based on clinical, pathologic and anatomic observations and demonstrated by an analysis of numerous transitional lesions between these two entities. Giant-cell tumors of the skull and long bones, epulides of the alveolar border and giant-cell xanthomos of the tendon sheaths were found to be fundamentally related to a transitional process characterizing the histogenesis of bone via the indirect route of substitution bone. This transition process underlying all these tumors, as shown by embryologic studies, involves a proliferation of giant-cell osteoclasts, the function of which is to initiate the canalization and vascularization of the preliminary calcified structure.

A Treatment of Persistent Bronchial Fistula.—POOL and GARBOCK (*Ann. Surg.*, 1929, **90**, 213) state that bronchial fistulas occur most commonly with empyema thoracis and lung abscess. The majority close spontaneously. Persistence of a fistula may be due to suppuration in the parenchyma of the lung or the bronchial tree, the presence of a rigid-walled empyema cavity with which the fistula opens, the formation of a bronchocutaneous channel or the presence of a foreign body. Operative closure of a bronchial fistula should not be attempted until the need for drainage of a lung suppuration has passed. Very small fistulas will frequently close following the local application of some cauterizing agent. For the closure of a bronchial fistula which persists in spite of conservative measures, an operative procedure is described. This consists in plugging the fistula with a pedunculated muscle flap. The operation is simple, of wide application and has proved successful in the authors' experience. The production of a bronchial fistula in an experimental animal is attended with great technical difficulties. Although the experimental data herewith reported do not duplicate exactly conditions as found in man, the results obtained indicate clearly the processes of repair following closure of a bronchial fistula by the method described. A muscle flap placed in a bronchial fistula to effect its closure remains viable and is not completely replaced by fibrous tissue.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Rectal Administration of Liver and Liver Extract in Pernicious Anemia.—PULVER (*Therap. d. Gegenw.*, 1929, **70**, 294) reports on his favorable experiences with the rectal administration of liver or liver extract. This channel of administration is indicated in patients unable to retain the orally administered liver or liver extract. The impetus for the study of this problem was the observations on two patients (reported before) with severe manifestations of pernicious anemia, who failed to respond with improvement after oral administration of liver, but who showed marked improvement when the liver was administered rectally. This method of administration consists of passing the crushed raw liver mixed with milk and 20 drops of tincture of opium through a sieve and introducing this mixture slowly through a high rectal tube after a preliminary cleaning enema. Instead of raw liver, correspondingly potent liver extract may be used. Liver extract suppositories were also used. It is advisable to leave the rectal tube inserted for some time and to remove it slowly and gradually. If the patient develops diarrhea the rectal administration should stop for a day or two. Most people retain the therapeutic liver enema well. Old people occasionally exhibit rectal pain because of the presence of hemorrhoids and diarrhea. The author reports his experiences on 11 patients. In conclusion he lays emphasis on the fact that the success of the liver therapy often depends on the amount administered. The optimal dose varies according to the individual patient and his condition. In rare instances as high a dose as 1 kg. of raw liver or equivalent liver extract may be required for prompt response.

Hemostatic Therapy in Hemophilia.—PAYNE and STEEN (*Brit. Med. J.*, 1929, i, 1150) investigated the effect of hemoplastin, "coagulin-Ciba," "fibrogen Merrell" (tissue fibrinogen), horse serum, protein shock, calcium, citrated human blood, and citrated human plasma on the coagulation time of 4 patients with hemophilia. None of the above agents exerted a permanent effect. The only form of treatment that was found to be of any real value was intravenous injection of either citrated whole blood or citrated human plasma. Citrated plasma given intraperitoneally or intramuscularly was without effect. Citrated human plasma has the advantage of not requiring a preliminary blood grouping, and the use of human plasma prevents any danger of anaphylaxis. Both

with whole blood and plasma no stage of hypocoagulability occurs. The authors conclude that the most effective agents, both for treatment and pre-operative prophylaxis, are citrated whole blood and citrated plasma given intravenously.

The Toxicity of Different Arsphenamin (Salvarsan) Solutions.—It is well recognized that the method of the preparation of arsphenamin solutions has an important bearing on the toxic and therapeutic effect of arsenical compounds in animals and in man. DREYFUS (*Münch. Med. Wchnschr.*, 1929, **1**, 1285) reports his clinical experiences with different solvents used in arsphenamin therapy.

Although the use of tap water as a solvent is tolerated by most patients without untoward symptoms, it cannot be recommended for general use. The presence of small amounts of potassium and magnesium salts in the tap water may increase the toxicity of arsphenamin. Occasionally, the presence of small solid particles may be the source of minute emboli. Redistilled water should, therefore, be preferred.

Animal experiments indicate that arsphenamin dissolved in sugar solutions is less toxic. For clinical purpose 15 to 40 per cent glucose solution proved very useful. The use of arsphenamin dissolved in 20 to 25 c.cm. of a 40 per cent glucose solution is especially indicated in: (1) patients who are hypersensitive to arsphenamin; (2) patients with cardiovascular diseases; (3) patients who after malaria innoculation have to receive large doses of neoarsphenamin as complimentary treatment. Instead of glucose, lactose may be used. Both glucose and lactose solutions are less toxic than watery solutions, although the therapeutic value of the arsphenamin is unchanged.

The use of a 10 per cent calcium chlorid solution as a solvent for neoarsphenamin is advocated in patients who are hypersensitive to this drug.

The author claims that the use of certain iodin solutions as solvents increase the therapeutic efficiency of arsphenamin.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

General Edema in Association with Tetany of the Newborn.—SHANNON (*Arch. Ped.*, 1929, **46**, 549) says that the term "Edema Neonatorum" has come into the minds of many to signify a rare disease entity occurring almost altogether in premature or immature infants and bearing in its fullest development little resemblance to ordinary edema. It has such a high mortality that when seen the prognosis is most unfavorable. In many textbooks this in the only reference made to edematous conditions occurring in the neonatal period. As a result,

an entirely wrong opinion is apt to be acquired concerning the edemas as they occur in the newborn. Some writers appreciating this fact have separated this condition entirely from the edemas of the newborn and consequently have given a much more accurate conception of the latter. Among these authors are von Reuss and Feer who recognize edema as one of the common affections of the newborn period without particularly serious significance. They attribute its occurrence to a deficiency in the salt-excretion function at this age. Since edema is a common condition in the neonatal period, not necessarily confined to premature and immature infants, the author feels that it is a grave error to use such a valuable a term as "Edema Neonatorum" for a rare disease complex which is so singularly unlike edema as it usually occurs. In this paper he reports three cases of generalized edema in newborn infants. In each of these the edema accompanied most generally symptoms of tetany and in each it disappeared promptly along with the tetanic manifestations under calcium and parathyroid therapy. This result was obtained in spite of the fact that two cases presented other possible causes of the edema which have been frequently mentioned as being responsible for edema in the newborn. One case had a congenital heart, while the other had definite evidence of kidney pathology. As a result Shannon feels that calcium deficiency may be one of the causes of generalized edema occurring during the newborn period. He also claims that tetany is common enough during this period for this cause to be frequently met. He also suggests the possibility that cerebral edema may be responsible for certain cyanotic attacks seen during the neonatal period.

A Soy Bean Preparation for Feeding Infants with Milk Idiosyncrasy.—Hill and Stuart. (*J. Am. Med. Assn.*, 1929, **93**, 985) remind us that soy bean flour was originally used in this country by Ruhräh in the form of a gruel in the treatment of diarrhea in 1910. Previous to that time it had been used in one form or another in China as a supplementary infant food for many years. In a case of milk idiosyncrasy under the care of Dr. Hill an attempt was made to prepare a dried infant food that would be complete in meeting the child's requirements and yet be free from animal protein. Soy bean flour was chosen as a most promising food from which to obtain the protein necessary. With the assistance of Dr. James L. Gamble a formula was devised that was satisfactory for the theoretical requirements of infants. Sufficient soy bean flour was used to give a protein percentage of 4 in the finished product and diluted food. This percentage, higher than that normally present in milk, was adopted because of the differences in the amino-acid content of the two proteins and in order to assure ample amounts of each of the necessary ingredients the salt content of cows' milk and soy bean flour was studied in order to determine the additional salts required. It was found that magnesium, potassium and phosphorus are present in sufficient amounts but that there is a deficiency in calcium, sodium and chlorin. In order to overcome this the addition of calcium carbonate, 2 gm., and sodium chlorid, 1 gm., was made for each 100 gm. of solids. The vitamin content of soy bean flour if properly prepared and cooked has been shown to be adequate by the studies of Osborne and Mandel. In order, however, to compensate for possible differences in the content

of the fat-soluble vitamins in different samples, which varies with the completeness or incompleteness of the removal of the oils in the preparation it was suggested that cod-liver oil be given regularly but it was not included in the composition of the food but is recommended to be used as an additional food substance along with orange juice. In order to meet the additional energy requirements the fat content of the food was raised by the addition of olive oil in quantities sufficient to make the final fat content in the diluted food 3 per cent and barley flour in quantities sufficient to make the final carbohydrate percentage about 4 per cent. Sugar was purposely omitted because it was felt that it would be better to leave the determination of the amount and kind of sugar to be added to the discretion of the physician so as to meet the needs of individual infants with varying degrees of tolerance for carbohydrate. The authors feel that sugar in some form should always be added unless the infant has sugar intolerance. This preparation has been used for a year to the entire satisfaction of the writers, who have observed that stools are likely to be somewhat more frequent than seen in babies on cows' milk but rarely amounting to diarrhea. In babies under eight months of age they have not started with the full strength formula but recommend two-thirds strength and in small babies it is advised to start at half strength. This concentration may soon be increased. In all, they report 40 babies fed on this food and remark that they have done well. They feel that they are not justified in stating that this milk is as good a food for infants in general as the ordinary formulas made from cow's milk but they do feel that it is a very efficient and practical substitute when it is impossible to use milk. This was especially noted in babies with eczema.

Epilepsy in Children.—McQuarrie and Husted (*Am. J. Dis. Child.*, 1929, **38**, 451) studied the superficial relationship between water balance and the occurrence of seizures in a number of epileptic children. There seems to be a tendency for the epileptic patient to retain water during the active phase of the disease in amounts which are harmful. Convulsions tend to occur when a positive water balance above a certain amount is established. When diuresis follows the attack further seizures are prevented temporarily. They could not state that the effect of the extra water is due solely to changes within the brain. Procedure such as fasting, the use of ketogenic diets and the stringent restriction of water with nonketogenic borderline diets led to partial dehydration of the tissues and prevention of seizures. They observe that the sudden increase of the water intake during treatment by dehydration caused recurrence of seizures at least in the severe cases. Parenteral administration of pituitary or of the antidiuretic hormone of the hypophysis caused the development of a positive water balance and the occurrence of seizures. Urea in large doses caused the loss of retained water. They feel that there is a definite relationship of water balance and the etiology of epilepsy.

The Relationship of Jaundice and Weight to Blood Values in the Newborn Infants.—Mitchell (*Am. J. Dis. Child.*, 1929, **38**, 518) made red cell counts and hemoglobin estimations of the blood of 69 infants on the first, third, seventh and tenth day of life. He also studied the

volume percentage of the cells in the blood in 50 newborn babies. He found that the cell volume was considerably greater than the average for adults and the volume index was also high. He found that infants with jaundice did not show lower average red cell and hemoglobin values than those without jaundice. Practically all babies showed a loss of red cells and hemoglobin between birth and the tenth day of life but the average loss of those with marked jaundice was only slightly greater than of those without jaundice. Changes in weight were accompanied by changes of red cells in infants showing the same degree of jaundice. Babies with marked jaundice showed a much smaller gain over their weight at birth than babies on the tenth day than babies without jaundice. Dehydration when of a degree to show clinical manifestations with fever showed a marked influence on the red cell count.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

R. L. GILMAN, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Drug Reactions from Barbital (Veronal) and Phenobarbital (Luminal).—POOLE (*Yale J. Biol. and Med.*, 1929, **1**, 345) states that within the last sixteen years, the barbital drugs have achieved a wide popularity and while the doses in recent years have been less than the former large doses, reactions still occur in upwards of 3 per cent of the cases (Menninger). There are two types of reaction, a general systemic reaction with signs of acute poisoning, and skin reactions with or without mild systemic disturbances. Most of the severe reactions have occurred after large doses, yet frequent reactions are reported in patients receiving but 1½ grains a day. Reactions occur within twenty-four hours, or as late as eighty-one days. The author reports 11 cases, 4 showing the skin type of reaction (all luminal cases) and 7 cases of general reactions (3 luminal and 4 veronal). The cases with severe general reactions had no dermatitis, while the dermatitis group showed a slight or moderate general reaction, such as fever, nausea, vomiting, diarrhea, headache, stomatitis and conjunctivitis. Leukocytosis and eosinophilia were often present. One of the skin reaction cases with an exfoliative type of dermatitis came to autopsy. The exfoliative reaction was found to involve the bronchi, kidney pelves and ureters, and the observer suggests that the mechanism of death in exfoliative dermatitis is bronchial obstruction and not bronchopneumonia. One of the reported cases was the occurrence of a skin reaction with moderate systemic symptoms

in a girl, aged fifteen years, who was taking both luminal and Fowler's solution. To determine the rôle of luminal in this instance an intradermal skin test was made. This was done using a 2 per cent aqueous solution of sodium luminal (hypodermic tablet). Approximately 0.02 cc. was injected intradermally on the flexor surface of the forearm with a control of physiologic saline on the other arm. Two minutes after the injection an urticarial wheal with pseudopod formation developed at the point of injection of the luminal solution. The wheal increased rapidly in size, remained unchanged in size for two hours and then gradually disappeared. The author concludes that the mechanism of the reaction in the poisoning cases is relatively clear but in the dermatitis cases, the relative infrequency, the type of skin rash, the blood picture and the reaction to intradermal skin tests suggests a drug idiosyncrasy, allergic in nature.

Concerning the Cultivation of Spirocheta Pallida.—KAST and KOLMER (*Am. J. Syphilis*, 1929, **13**, 419) report their failure to cultivate Spirocheta pallida from human and rabbit lesions, despite numerous and persistent attempts for a period of five years. In all, sixteen different culture media were employed, all the media were incubated for from one to three days before inoculation, all were kept at 37° C. and all but two were sealed with vaselin after inoculation. In their work no true multiplication of spirochetes occurred in any medium. Saprophytic spirochetes, simulating Spirocheta pallida, could be cultivated. In reviewing the literature from 1906 to date, the authors feel that with the exception of Noguchi's work possibly many of the reported cases of alleged Spirocheta pallida cultivation were in reality cultures of a finer saprophytic type. A comprehensive and detailed abstract of the work of thirty-three investigations from the literature is included.

Febrile Body Temperatures as Possible Adjunct Treatment in Wassermann-fast Syphilitic Patients.—CADY and EWERHARDT (*Am. J. Syph.*, 1929, **13**, 313) conducted a series of hot baths on 13 patients with syphilis. With one exception all the cases were of the chronic type and designated Wassermann-fast. The bath temperatures varied from 104° to 107° F. at the outset with subsequent bath temperatures of 104° to 111° F. The body temperature rose to 102.3° to 106° F. in twenty to forty minutes. In general the bath was continued at the highest tolerated temperature for twenty to forty minutes. The pulse rate rose in proportion to the body temperatures. No serious adverse reactions were encountered. The authors present their data in the form of thirteen complete histories and protocols with no general tabulation of results. Their investigations did not reveal any consistent evidence that hot baths were useful in Wassermann-fast patients. They believe that the serologic reactions were rendered more labile during relatively short periods of thermotherapy. The fact that there was an improvement in the patient's sense of well-being and an apparent serologic response in a small percentage of their cases has encouraged the investigators to continue their investigations on this mode of therapy.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Radiation Treatment of Fibromyomata.—Although the radiation treatment of uterine fibromyomata is now firmly established in the properly selected cases, a large series of such cases is always worthy of at least passing notice. In a series of 604 cases which have been treated by SOILAND, COSTOLOW and MELAND (*California and West. Med.*, 1929, **30**, 234) by means of radiant energy including low voltage Roentgen ray, high-voltage Roentgen ray, radium alone and radium with Roentgen ray, they were able to trace 562 patients and have tabulated their results, which were quite satisfactory. In 5 cases in younger women with small fibroids who gave dysmenorrhea as their only symptom and had a return of their menstruation after the treatment, four were found to be entirely relieved of the dysmenorrhea. In only 1 case in the series was pregnancy associated with the fibroid tumor and she miscarried, but she had a positive Wassermann and had miscarried three times previously. They believe that it takes some time for the complete disappearance of the tumor mass, probably about five years. Bleeding continued in 10 cases, necessitating a hysterectomy; 6 of these proved to be malignant (carcinoma of the fundus). In the entire series of 562 cases only 13 (2.3 per cent) failed to respond to the treatment. It is their experience that the combination of radium and deep Roentgen ray therapy is the best type of radiation treatment in the majority of cases. While radiation is the treatment of choice in tumors not larger than a four-month pregnancy, they state that the majority of tumors larger than this size may be rendered symptomless by this treatment. This is worth remembering in the presence of a large bleeding tumor in a patient who is not a fit subject for surgery.

Intraäbdominal Insertion of Radium in Cervical Cancer.—In an attempt to eradicate deeply situated carcinomatous infiltration resulting from cervical cancer, DONALDSON (*Brit. Med. J.*, 1929, i, 844) has developed a technique for the intraäbdominal application of radium. This is usually carried out about six to eight weeks after the vaginal application, that is to say, when the local growth has disappeared and all the ulceration has healed. No attempt has been made so far to combine the intraäbdominal application at the same time with the vaginal treatment merely on the theoretical grounds that while there is an infected area in the cervix and fornices it is not wise to do anything to the abdomen and parametrium which might lower the resistance to that infection. The patient is put into the Trendelenburg position and

the abdomen is opened. A general examination is made of the liver and aortic glands in addition to the pelvic organs and the iliac glands. The intestines are packed off and the uterus is pulled forward; the parietal peritoneum is then picked up with forceps and the radium needle inserted, leaving only the eye of the needle protruding from the peritoneum. A suture is placed through a small portion of peritoneum below the level of the needle eye and the knot is tied over a glass bead to prevent cutting through the thin peritoneal tissue. Other radium needles are placed at a distance of from 1 to 1½ cm. from each other, starting at one sacroiliac synchondrosis and ending at the corresponding joint of the opposite side. In addition, four or more needles are placed in front of the broad ligaments in the hope of eradicating the disease from the obturator glands. The ends of the ligatures are tied together and pushed down into the pouch of Douglas. The abdomen is completely closed and the radium left *in situ* for seven days. At the end of this time the abdomen is again opened and the radium is removed. An objection to this technique is the second laparotomy at the end of a week, but up to the present it has been felt that in order to keep them in position the needles should be sutured to the peritoneum which makes it impossible to pull them out. In addition to this they are often placed at an angle to the line of traction and damage might be done if they were pulled out blindly.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Light Deficiency as the Principal Cause of Osteomalacia in India.—Osteomalacia is known throughout India, and is especially severe in Kashmir, where almost all the better class of women are more or less affected. In her paper VAUGHAN (*Brit. J. Actinotherapy and Physiotherapy*, 1929, **3**, 243) shows that this condition is due to want of light. The disease begins at puberty or before and roughly coincides with marriage. It commences with vague pains in the bones and backache, and is often mistaken for rheumatism. The girl is always anemic and frequently complains of spasm of the hands. Digestion is bad. Gross changes are exhibited in the bones of the limbs which become bent and twisted. In the pelvis, which becomes soft like wax, the bones are pressed together laterally by the heads of the femora until the pubic rami are almost in apposition, the space between the ischial tuberosities is greatly reduced, the lower lumbar vertebræ are displaced forward, and childbirth becomes impossible. The women in India who suffer from osteomalacia are those whose social customs make it imperative

for them to live indoors. She can never go out and sees but few people. If her husband is poor she remains behind a curtain in the back of his one room, completely deprived of light and air, or she may have a dark room with no window. The pains of osteomalacia are worse in the winter and improve in the summer, in the Kashmir valley. In the winter the women of this class cover their lattice windows with oiled paper or hang felt rugs over them. There is little sunlight and the valley is shrouded in mist and fog. It is important to note, on the other hand, that among the poorer classes of Kashmir who work in the open air such a condition as osteomalacia is unknown; the women are healthy and easily bear from 8 to 20 children.

Rugæ Gastricæ: Their Importance in Roentgenologic Diagnosis.—The study of the gastric rugæ, according to GOLOB (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 33) is a much neglected field, yet it may assist materially in gastroenterologic diagnosis. For their demonstration it is necessary that the amount of barium in the region examined be relatively small. The examiner may use either a small quantity of the contrast meal, or a thin suspension of barium, or thin out the usual dense mixture by manual pressure over the median and prepyloric segments of the stomach. Lenk and Eisler have shown that the rugæ in the immediate vicinity of an ulcer are not parallel, as normally, but converge toward the ulcer. Distortion or localized effacement of the rugæ usually bespeaks induration or infiltration of the mucosa. This sign is especially important when it is associated with a localized absence of peristalsis. In the cardiac region of the stomach, distortion of the rugæ, coupled with deformity of the gas bubble, practically clinches the diagnosis of an organic lesion.

Roentgen Diagnosis of Intrathoracic Neoplasms.—Pulmonary cysts of congenital origin, teratomata, dermoids and unruptured hydatid cysts present quite characteristic roentgenologic appearances, according to FARRELL (*Radiology*, 1929, **13**, 1). Mediastinal tumors of lymphatic origin are also fairly characteristic; they respond well to Roentgen therapy, and an exposure to a therapeutic dose of Roentgen ray may make possible a differential diagnosis between these tumors, substernal thryoid and extrabronchial carcinoma. Metastases of some varieties, notably the nodular and miliary, are readily diagnosed. Infiltrative and massive changes in the lungs, while not always definitive of themselves, are pathognomonic when associated with a known primary malignant tumor of some other organ. Extrabronchial pulmonary carcinomata, while they usually have characteristics which establish them as new growths, may be confounded with mediastinal lymphatic tumors. Endobronchial (bronchial) carcinomata present the greatest problem in the diagnosis of intrathoracic tumors. The signs which they present depend on their age and point of origin. The direct sign of endobronchial carcinoma is a mass due to the presence of a tumor, to which collapse, infection or metastasis may be traced as secondary phenomena. The indirect signs are similar to those of bronchial foreign body.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Further Light on the Transmission of Pain and Temperature within the Spinal Cord: Human Cordotomy to Abolish Pain Sense without Destroying Temperature Sense.—STOOKEY (*J. Nerv. and Ment. Dis.*, 1929, **69**, 552) presents 4 cases in which cordotomy was performed for the relief of intractable pain. Two had unilateral and 2 had bilateral cordotomies. The operation is performed in the unilateral cases through a Taylor's hemilaminectomy. A small, straight, knife is used. "A delicate lateral incision just ventral to the dentate ligament is made and the knife brought out just lateral to the ventral horn. By varying the depth of the incision, one may vary the segmental level of the anesthesia, since apparently the more distal segments lie nearest the periphery of the cord." In none of his cases was temperature sense involved after operation. He concludes that the pain sense is carried in the lateral spinal thalamic tract and that temperature sense is carried in a tract more ventrally placed, which may be the ventral spinal thalamic tract. He prefers the use of the small, straight knife in the operation because the sickle-shaped knife recommended by Fraser cuts a considerable amount of cord substance beyond that necessary and does not permit of accurate control of the incision.

Industrial Psychiatry.—ELKIND (*Mental Hygiene*, 1929, **13**, 378) calls attention to the contributions psychiatry has made to industry in diminishing the number of compensation neuroses, in the study and treatment of industrial poisoning and in the detection of malingering. In the management of industrial personnel the psychiatrist concerns himself with normal people. Here the main consideration is one of adaptation of an individual to his position, where generally a new adjustment may be necessary. He cites Anderson's work as an example of the fact that it is not only in the field of selecting that psychiatry may be applied, but also in the follow-up supervision of the individuals during their periods of adjustment and readjustment in the industry. He cites a few cases illustrative of readjustment of individuals who had difficulties at work.

Ueber Tetanie und Tetaniepsychosen.—FUNFGELD (*Archiv f. Psychiat. u. Nervenkrankh.*, 1928, **84**, 363) presents 9 cases of tetany with psychic manifestations, which were treated by meat-free diet including ¼ to ½ liter of milk and 30 to 40 tablets of hemokrinin per day. In all of the cases the symptoms of tetany were found to be

correctable by this treatment. The psychic changes which he found to belong properly to the tetany syndrome were very closely related to the epileptic form of mental changes. He concludes that the tetanic attacks have a motor component of the extrapyramidal type and that the extrapyramidal system has an affinity for the parathyroid disturbances.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Pathology of Hemangioma of Bone.—Bucy (*Am. J. Path.*, 1929, **5**, 381) reports 7 cases while previously Toepfer claimed that the condition was present in about 12 per cent of autopsies. The lesions consist of a hard mass within the medulla which at times may show a soft and even pulsating center. They bleed profusely. The mass consists of large cavernous spaces filled with blood, and supported by bony trabeculæ which show both degenerative and formative changes. Occasionally the endothelial character of the structure is suggested by the abundance of the foam cells. The author is uncertain whether these lesions are neoplasms or vascular malformations.

Spontaneous Rupture of the Aorta.—Lifvendahl (*Arch. Path.*, 1929, **8**, 200) reviews the literature upon spontaneous rupture of the aorta, a term restricted to the condition of loss in the continuity of the vessel wall occurring without evidence of extrinsic pathologic changes, trauma, or formation of an aneurysm with secondary mural perforation. The author reports 3 cases of the condition, which came to autopsy in patients of middle age who suffered from hypertension, cardiac hypertrophy and from varying degrees of renal involvement. The Wassermann reaction of the blood was negative in the first 2 instances and not examined in the third. In the first case a triangular-shaped tear, 3 cm. above the valve involving the entire circumference of the aortic wall resulted in an effusion of blood which stripped up the intima and perforated the adventitia to fill the pericardial sac. In the second instance, the aorta evidenced only a few fatty plaques on its smooth intimal surface, yet presented a transverse slit in the intima and media two finger breadths above the aortic ring. An opening of pinhead size in the outer aortic wall permitted the extravasation of blood into the pericardium. The third case presented three tears in the aortic wall; the first opening into the pericardium, the other two being situated in the abdominal aorta. In each of the 3 cases reported, histologic examination of the aortic wall at the site of the lesion revealed typically

syphilitic changes. Spontaneous rupture of the aorta most frequently occurs at the points of relative fixation, one and a half finger breadths above the aortic cusps or in the region of the ductus Botalli. The author wishes to emphasize the fact that while gross changes at the site of a rupture are frequently inadequate to explain the tears, localized microscopic alterations of a syphilitic or degenerative nature may be marked.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

The Oral Administration of Derivatives of Chaulmoogra Oil in Leprosy.—WAYSON and BADGER (*U. S. Pub. Health Rep.*, 1928, **43**, 2883) are cautious in expressing any opinion on the value of chaulmoogra oil preparations in leprosy, but point out disadvantages of the drug and its derivatives as ordinarily given. The writers employ an emulsion of the esters derived from the oil prepared by the use of acacia and syrup and cod-liver oil. The dose varies from 1 to 10 cc. per day, and the preparation usually is well tolerated.

The Thyroid Gland and Communicable Diseases.—A study of the effects of communicable disease upon the size of the thyroid glands of elementary school children made by OLESEN (*U. S. Pub. Health Rep.*, 1928, **43**, 3009) revealed the following: (1) Thyroid examinations of 589 boys and 636 girls were made before and after communicable illnesses. After the illness no changes in thyroid size were detectable among 51.7 per cent of the boys and 45.6 per cent of the girls. Thyroid size was decreased in 13.8 per cent of the boys and 11 per cent of the girls. Increased size was noted among 34.5 per cent of the boys and 43.4 per cent of the girls. (2) The thyroids of 1842 boys and 1783 girls who did not have communicable illness in the interval were examined one year apart. No change in thyroid size had taken place among 48.4 per cent of the boys and 43.6 per cent of the girls. Thyroid size had decreased in 12.7 per cent of the boys and 18.6 per cent of the girls, while an increase was recorded among 38.8 per cent of the boys and 35.7 per cent of the girls. (3) A communicable disease census of 7977 boys and 8441 girls showed little difference in percentage incidence among the thyroid-normal and thyroid-enlarged children who had the same maladies. The author concludes from his findings that there is some evidence to show that one of the immediate effects of communica-

ble diseases among girls of elementary school age is simple enlargement of the thyroid gland. However, this thyroid enlargement appears to be temporary in character. A comparatively short time, the length of which is as yet undetermined, after a child recovers from a communicable disease, he is no more prone to changes in thyroid size than a child who has not had a communicable disease. In so far as elementary school children are concerned, there appears to be no ground for assuming that the ordinary communicable diseases are responsible for simple goiter. The underlying causes of this malady must be sought for in other directions.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 21, 1929

Some Remarks on the Chemistry of Cell Division.—FREDERICK S. HAMMETT (from the Research Institute of the Lankenau Hospital, Philadelphia). Cell division is an expression of reactions between chemical molecules. From this point of view the process is obviously self limited. The problem of the chemistry of cell proliferation therefore resolves itself into an inquiry as to the nature of the key group initiative of cell multiplication and which by its reaction products is inhibitive thereof.

Pb-ion was used as the reagent. It was found that the metal retards development of parts where growth by increase in cell number is most active in chick embryos[1] and root tips of seedlings of beans and corn.[2] The seedlings showed that this is due to inhibition of mitosis and not of growth by increase in cell size.[3] Chemical studies under the microscope brought out that a Pb compound is deposited in the region of active cell proliferation,[4] and that it is concentrated in the nucleus[5] particularly in association with cells undergoing division.[6] Chemical analysis of the deposit under the microscope and in the test tube showed it to be a combination of the metal with sulfhydryl.[7] Further it was found that –SH is concentrated in regions of active growth by cell multiplication. The hypothesis followed that sulfhydryl is specifically essential for growth of this type and that this is stopped by Pb because of removal of the activating group.

This hypothesis was tested by observing cell proliferation and cell size reaction in root tips and paramecium to thio-glycollic acid, di-thio-di-glycollic acid, cysteine, cystin, glutathione, ergothioneine, and insulin. As controls the equivalent compounds minus the –SH group were used when known. Experiments with thio-glucose on wound healing in rat and man were also done.[8] In all cases where labile –SH was present, acceleration of cell proliferation obtained, and no stimulation of cell growth in size. The work as a whole, then, establishes the fact the the sulfhydryl group is specific and essential to cell growth in

number.[9] Details as to methods of procedure are to be found in the papers cited.

If the premises stated at the beginning be correct, it should be expected that, according to the law of mass action, the products of reaction of the effective group would be inhibitive of cell proliferation. Recent experiments with oxidized products of thio-glycollic acid, thio-glucose, and other simple sulfhydryl derivatives show this to be so. The data so far, then, justify the conclusion that cell division is regulated by a chemical equilibrium in which -SH is the key group.

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Gastric Motility Studies—Ruminant Stomach.—R. S. AMIDON (from the School of Veterinary Medicine, University of Pennsylvania). The physiology of digestion as it occurs within the ruminant stomach has received but a limited amount of experimental study. Such data as are available today represent the investigational effort of but a limited number of workers whose studies have been conducted three to eight decades ago. The contributions of Colin, Flourens, Chauveau, Toussaint and Ellenberger are among the most important and have to serve to clarify many of the problems encountered in this interesting field of physiology, especially as regards the mechanics of the digestion process.

In 1921 the author, collaborating with Dr. A. F. Schalk of the North Dakota State College, undertook a study of the motility factors for the purpose of reviewing and enlarging if possible upon the existant experimental data pertaining to this subject. The ox was selected as the experimental subject. A gastric fistula 4 to 6 inches in diameter was established in the left flank region of each animal, this opening communicating with the first and second divisions of the compound stomach. These large fistulæ did not disturb the normal body functions in any appreciable manner some of the animals being kept under observation for a period of two years. It was of course quite essential that the fistulæ be closed whenever observations were not in progress. This was accomplished by a special valve-like device constructed of wood and leather which served to guard against any serious loss of gastric contents and the effects of cooling and drying of the gastric mucosa. Observations were secured by means of graphic records, palpation and visual inspection. The third (omasum) and fourth (abomasum) divisions of the stomach were not freely accessible to study and the data secured relate chiefly to the functional activity of the first (rumen) and the second (reticulum) portions of the organ.

The most important results obtained from this study are as follows:

1. Details were secured concerning the frequency, sequence, etc., of the contractions in the four divisions of the stomach.

2. The source of the material forming the bolus of rumination was definitely proved to be from the reticular cavity.

3. The esophageal groove is nonfunctional in mature animals but is active and serves to guide milk into the abomasum of the nursing calf.

4. Pressure and friction stimuli when applied to the gastric mucosa per fistula will initiate the act of rumination. Such stimulation is probably representative of the effects exercised by the heavy coarse food material taken into the rumen and reticulum.

5. No digestive secretions are elaborated in first three divisions of the ruminant stomach. Fermentation, which occurs in a very active manner within the rumen and reticulum, releases valuable nutritive materials from their cellulose investments so that the digestive secretions of the abomasum and intestinal region are enabled to accomplish their action.

6. The importance of abundant moisture within the stomach has been especially emphasized in this work and has a practical significance in the treatment of rumen impaction.

The Effect of Posture on the Cardiac Output.—Isaac Starr, Jr., and Leon H. Collins, Jr. (from the Laboratory of Pharmacology of the University of Pennsylvania). Two series of experiments have been completed to extend the use of the improved ethyl iodid cardiac output method (Starr and Gamble, 1928) to normal subjects standing at rest. These experiments demonstrate that:

1. In the standing position the ethyl iodid content of arterial blood may be estimated from the content of alveolar air collected automatically (five experiments).

2. If a standing subject, after inhaling ethyl iodid, rebreathes for thirty seconds in one bronze bag, then for a minute longer in a second bag, the agreement between the ethyl iodid content of the two bags is not as close as in the supine position; that of the second bag averaging 13.6 per cent below that of the first. Therefore the equilibrium between the ethyl iodid in mixed venous blood and that in air rebreathed for thirty seconds cannot be so closely demonstrated as in the supine position. However any error in estimating ethyl iodid in mixed venous blood must be small and in the direction of making the calculated bloodflow smaller than the actual in the standing position.

Ten duplicate determinations of cardiac output in both the standing and supine positions have been made on five subjects. In four subjects no significant change of cardiac output followed the change from supine to standing position or the reverse (seven experiments). These results are similar to those of Grollman. In one subject the bloodflow standing was always significantly less than that lying (three experiments). This subject had a history of occasional fainting without obvious cause, the others had no such history.

If the results are calculated from our data according to the method of Henderson and Haggard the cardiac output always appears much smaller in the standing than in the lying position. The addition to this calculation of the factor representing the ethyl iodid content of venous blood brings the result in both positions to the same figure in four of our five subjects.

A Comparison of the Histology and Physiology of the Sensory End Organs of the Prepuce.—R. G. WILLIAMS, B. MCGLONE and H. C. BAZETT (from the Department of Physiology, University of Pennsylvania). *Histological.* When pieces of skin are stained with methylene blue and cleared in oil of wintergreen it is possible to observe large numbers of nerve endings and to determine their depths and relations without recourse to sections and reconstructions.

The following data were obtained from skin removed at circumcision which had been treated in such a manner. The data presented represent a study of one square centimeter of skin. Studies on other square centimeters show no appreciable variation from the one given.

One square centimeter of skin contained 212 nerve endings which were quite evenly distributed. Of this number there were seven types: 115 were free endings which occurred at a depth of 56 to 72 micra; 52 were very small end bulbs having a very fine net arrangement but no capsule and occurring at a depth of 20 to 28 micra; 23 were free endings having a brushlike arrangement at the end of numerous branches and being at a depth of 40 to 60 micra; 15 were the so-called Krause endings which occurred at a depth of 64 to 72 micra; 4 were an unusual type having a thick, pale capsule and a central nerve core which occurred at a depth of 92 to 140 micra; 1 corresponded to Ruffini's ending at a depth of 200 micra; and one was a Meissner ending which lay at a depth of 140 micra.

The normal thickness of the skin in this region being 0.6 mm. the shrinkage of this specimen was 30 per cent. When the figures are corrected for shrinkage the depths of the end organs would appear to be as follows:

Type I	80–103 micra
Type II	28.6–40.0 micra
Type III	57.1–85.5 micra
Type IV (Krause)	91.4–103 micra
Type V	131–200 micra
Type VI (Ruffini)	285.7 micra
Type VII (Meissner)	200 micra

A determination of the depths of the bloodvessels of the prepuce from a completely injected and cleared specimen indicates that in general the Ruffini end organs lie in the deep rete venosum of Spalteholz, those of Meissner lie in the superficial rete venosum, and the Krause endings lie in the arteriovenous region immediately below the corpus papillæ of the corium.

Physiological. A fold of tissue covered on both sides with skin is obtained by suspending a part of the prepuce or a fold of loose skin from the dorsal surface of the penis by two hooks connected to weights (30 gms.) over pulleys. The sensitive spots are mapped. It is found possible to stimulate the end organs sensitive to temperature from either side, though the latency of sensation is less, when the stimulus is applied to the spot nearer to the end organ. The thickness of the fold is determined from Roentgen ray photographs, the time of thermal penetration by the use of thermocouples, and comparison with the latencies of sensation permits calculation of the probable depths of the end organs involved.

Touch. The threshold for touch has been a pressure of about 1.5 gm. per mm. radius, applied with a hair (von Frey's technic). The reaction time to touch sensations is in this area very variable; the minimum has been 0.11″ to 0.14″ (3 subjects); the median value has varied from 0.25″ to 0.31″.

One square centimeter of skin ruled in sq. mm. areas (rubber stamp) gives positive responses to touch stimuli (2 gm. per mm. radius) in 31 to 64 per cent of the squares tested.

Cold. The reaction times are variable—the minimum recorded was 0.23″. The cold spots are distributed irregularly. When determined with a point of 1.5 mm. diameter their number varies between 2 and 11 per sq. cm. When mapped more carefully with a cooled wire of $\frac{1}{3}$ mm. diameter the maximum number observed has been 12 per sq. cm. Calculation of depth from variations in reaction time indicates a value of 0.1 mm. as the most probable.

Warm. The reaction times are less variable than those of cold, the minimum recorded was 0.40″. The warm spots are usually related to visible veins. Their number varies between 0.5 to 2 per sq. cm., with a median value of 1 per sq. cm. The calculated depth is most commonly 0.35 mm.; occasionally depths of about 0.5 mm. are estimated. The total thickness of a double fold has usually been 1.2 mm.

Both with warm and cold there is no doubt that stimulation can be induced from either surface, even though thermal gradients must be quite different. At the depths estimated for the end organs vascular plexuses probably exist; it has appeared easier to stimulate cold and warm end organs by lateral transmission of thermal changes when the application is made distally as estimated by the direction of the veins. Conduction along the blood stream is probably an important factor.

We would like to express our thanks to Dr. H. Strughold for assistance in some of the experiments and for instruction in technical methods employed in von Frey's laboratory.

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